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Drinking Water Criteria
Document for Barium (Final Draft)

Life Systems, Inc., Cleveland, OH

Prepared for

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The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on barium. This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of barium
- Toxicokinetics and human exposure to barium
- Health Effects of barium in humans and animals
- Mechanisms of toxicity of barium
- Quantification of toxicological effects of barium

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I. SUMMARY

Barium is a highly reactive element that occurs in nature in the combined state. The most common minerals of barium are barite ($BaSO_4$) and witherite ($BaCO_3$). These are relatively insoluble in water, but other salts are readily soluble (e.g., $BaCl_2$, BaS, $Ba(NO_2)_2$). Barium compounds are used commercially as pigments and in the manufacture of rubber goods, photographic paper, X-ray contrast material, brick and ceramic products, glass, plastic, pyrotechnics, oil additives and steel. Atmospheric barium is the result of industrial emissions, fossil fuel combustion and entrainment of soil and rock dust into the air. Barium is also present in seawater, fresh water and edible crops. Food represents a primary source of barium for the general population.

Barium is absorbed via the nasal mucosal membranes, lungs and gastrointestinal (GI) tract. Soluble barium salts are absorbed most readily (3% to 11% of $BaCl_2$), but even the less soluble carbonate and sulfate salts of barium are absorbed (45% and 85% of absorbed $BaCl_2$ dose, respectively). Gastrointestinal absorption of barium in animals varies widely (from 5% to 85%), depending on the species, contents of the gastrointestinal tract and age. Absorption in fasted rats (six to eight weeks old) was three times that of fed rats. Weanling rats absorbed 85% of an oral dose of barium, while adult rats absorbed approximately 7%. A milk sugar (lactose) and lysine significantly ($P<0.05$) increased barium absorption in fasted adult rats. The International Commission on Radiological Protection (ICRP) Committee II Report on Permissible Dose for Internal Radiation reported a gastrointestinal absorption factor of 5% for reference man. The National Academy of Sciences (NAS) Safe Drinking Water Committee has evaluated the available limited data and estimated that 20% represents a conservative estimate of the gastrointestinal absorption for barium in humans. However, no definitive barium absorption studies in humans were located in the literature. Information is specifically lacking on barium absorption in human children to determine if the observations in young and adult rats apply to the human.

Absorbed barium is distributed via the plasma to soft tissues and to bone and maximum concentrations are achieved within three hours after dosing. It may also cross the placenta and reach the fetus in pregnant mammals. Barium is rapidly cleared from the plasma, and barium content in soft tissue closely parallels the barium concentration in plasma. Exceptions are the salivary gland, melanin-containing tissues, cardiac muscle and bone, all of which may retain barium.

Retention of barium after exposure is primarily due to skeletal deposition which occurs preferentially in active areas of bone growth (tibia ends) and on bone surfaces. The metabolism of barium closely parallels that of calcium, but the skeletal accretion rate for barium is approximately twice that for calcium. A 70-kg human contains approximately 22 mg of barium, 90% of which is located in bone.

Age or sex differences in tissue barium content in humans are not apparent. Tissue barium content does vary with geographical location.

Long-term barium balance studies in humans have indicated that homeostatic mechanisms may maintain an equilibrium between barium intake and excretion.

Excretion is primarily via the feces. The ratio of total fecal to urinary excretion is approximately 9:1. It has been reported that minor amounts of barium are excreted in seminal fluid and saliva (0.81% and 0.22%, respectively, of a single intravenous dose administered to a 60-year-old human) and in the milk of lactating cows (0.6% of a single oral dose).

The principal routes of barium exposure in humans are drinking water, food and air. Water concentrations of barium are generally below 0.2 mg/L. However, approximately 150,000 people in the U.S. on public water systems are supplied with water containing more than 1.0 mg/L. Barium intake from the diet is reported to be 0.75 mg/day (0.67 mg/day excluding drinking water). Intake of barium from the air ranges from 0.09 to 26 μg/day. Thus, people drinking low barium water (0.2 mg/L or less) receive the greatest part of their barium intake from food, but the situation is reversed when high-barium water (1.0 mg/L or greater) is consumed.

Animal studies indicate that barium exhibits a steep toxicity curve and that the acute lethal dose of barium varies with the compound, route of administration, species, strain and age. For example, the oral LD_{50} for $BaCl_2$ varies from 132 mg Ba/kg to 220 mg Ba/kg for rats and is approximately 69 mg Ba/kg for mice. By contrast, the intravenous LD_{50} for $BaCl_2$ in mice has been reported to vary from approximately 8 to 19 mg Ba/kg. These data demonstrate the significant impact of route of exposure (i.e., GI absorption rate) on the effects observed at a specific exposure level.

Chickens tolerated up to 1,000 ppm barium in food (approximately 2,625 mg/kg) for three weeks with no adverse effects. Rats exposed to $BaCl_2$ in drinking water with up to 250 ppm barium for 13 weeks (total barium dosage of 3,433 and 4,114 mg/kg for males and females, respectively) showed no changes in physiologic parameters. The barium content of bone increased from 8 μg/kg in control animals to over 200 μg/kg in both males and females receiving water with 250 ppm barium. This level was achieved after four weeks of exposure, and was not increased further when measured after 8 or 13 weeks exposure. A study in female rats exposed to barium in drinking water indicates no effect on weight gain, tissue barium content or mean systolic blood pressure at 1 ppm for 1 to 16 months (approximately 0.071 and 0.051 mg barium/kg/day). Animals exposed to 10 ppm barium were observed to have very small but significant ($P<0.01$) increases in mean systolic blood pressure of 6, 7 and 4 mm Hg over controls 8, 12 and 16 after eight months of exposure, respectively, (0.60, 0.57 and 0.51 mg barium/kg/day). After one month of exposure to 100 ppm barium (7.1 mg barium/kg/day) the animals had a significant increase ($P<0.001$) in mean systolic blood pressure which averaged 12 mm Hg after one month. Systolic blood pressure in the 100 ppm barium group was consistently increased during all subsequent measurements, reaching 16 mm Hg over controls at 12 and 16 months (approximately 5.7 and 5.1 mg/kg/day, respectively). Cardiotoxic effects at 100 mg/L were also noted. This study demonstrates a dose-response relationship between barium exposure in drinking water and the development of hypertension and cardiotoxic effects in female rats. The NOAEL indicated by this data is 10 mg/L (0.51 mg Ba/kg/day), since rats exposed to this concentration of barium in drinking water developed only a slight increase in mean systolic blood pressure (4 mm Hg) in 16 months.

Inhalation of barium ($BaCO_3$ dust) for one month by rats produced elevated arterial blood pressure, changes in red and white blood cell counts, decreased weight, and reproductive and embryotoxic effects. However, chronic exposure of rats and mice to 5 mg Ba/L (approximately 164 mg Ba/kg for rats and 587 mg Ba/kg for mice) as the acetate in drinking water produced only proteinuria (males) and decreases in fasting serum glucose and increases in cholesterol increased (males and females) in rats and a slight decrease in longevity in mice. No increase in tumor incidence (determined by macroscopic examination) was apparent in these animals. Toe growth was inhibited in 50% of surviving chick embryos (18th day of incubation) when a single 20-mg dose of $BaCl_2$ was injected on day eight. Two in vitro assays used to identify possible mutagens were negative for barium. No other studies determining the teratogenicity, mutagenicity or carcinogenicity of barium were located in the literature.

Symptoms of acute barium toxicity in humans after oral ingestion are similar to those produced experimentally in animals by intravenous infusion. Most symptoms reflect pronounced stimulation of cardiac, smooth or striated muscle. Effects on the cardiovascular system include premature ectopic ventricular contractions, leading progressively to tachycardia, ventricular fibrillation and death. Hypertension is also common, stemming from increased cardiac contractility and/or increased peripheral resistance (arteriolar constriction). Hypokalemia occurs as a result of abnormal potassium permeability (see below). Gastrointestinal abnormalities include salivation and diarrhea. Skeletal muscles are initially stimulated, but later enter a state of flaccid paralysis.

The acute threshold toxic dose of barium for humans is estimated to be 0.2 to 0.5 g, or approximately 2.9 to 7.1 mg/kg for a standard 70-kg person. Chronic human inhalation exposure to barium carbonate ($BaCO_3$) or "soluble" barium produced no apparent adverse health effects. A study in South Wales reported a negative association between barium at 0.042 mg/L in drinking water and congenital malformations.

Epidemiological studies have shown an inverse correlation ($P<0.05$) between the occurrence of barium in drinking water (0.002 mg/L to 0.260 mg/L) and cardiovascular deaths. Another study compared two communities in Illinois having barium drinking water concentrations of 0.1 mg/L and 7.3 mg/L. No significant ($P>0.05$) differences were found in the prevalence of hypertension or cardiovascular, cerebrovascular and renal diseases. Thus, 7.3 mg/L is judged to be a NOAEL from this study.

A retrospective mortality study compared the incidence of cardiovascular deaths in communities with high (2.0 to 10.0 mg/L) and low (0.0 to 0.2 mg/L) barium concentrations in the drinking water. The death rate for both males and females was significantly higher ($P<0.05$) in the high-barium communities for all cardiovascular deaths, heart disease and all causes. A separate analysis revealed significant differences ($P<0.05$) in female deaths from all causes and male deaths from all cardiovascular diseases.

Most of the toxic effects of barium ion appear to follow from its effects on potassium fluxes in excitable cells (nerve, skeletal muscle, smooth muscle, heart). Exposure of such cells to barium ion results in a rapid decrease in potassium permeability and efflux. This leads to a decreased resting membrane potential, with resulting hyperirritability and increased activity. In the heart, extra-nodal cells may begin to depolarize spontaneously (leading to premature ventricular contractions), and abnormalities in the ECG become evident. Because potassium uptake by cells is stimulated by barium ion, there follows a large net flux of potassium from extracellular fluid into cells, resulting in marked hypokalemia.

Higher doses of barium inhibit neurotransmission and produce a progressive onset of paralysis, which correlates well with production of hypokalemia. All signs of acute barium toxicity except hypertension are alleviated by intravenous potassium administration. Hypertension appears to result from a direct action of barium on the heart and/or the resistance vessels. Barium ion also increases the secretion of calcitonin and adrenal catecholamines. This seems to result from barium ion entry into the secretory cells where it mimics the stimulatory affects of calcium ion.

Due to the absence of suitable data, neither a one-day nor a ten-day Health Advisory (HA) value has been calculated. An AADI of 1.79 mg/L has been calculated, based on a study of barium-induced hypertension in rats.

The standard for waterborne barium is 4 mg/L in the USSR. The existing MCL for barium in drinking water is 1 mg/L (USEPA 1976). The MCL for barium was derived by extrapolation from the threshold limit value (0.5 mg/m^3) for airborne barium nitrate, based on a 90% GI absorption factor and a 2 L/day water intake. Re-evaluation of data on GI absorption of barium from drinking water has resulted in newer estimates of 7% to 20% for adults and up to 85% for children.

Several groups warrant special consideration because of potential increased sensitivity to barium. These groups are: (a) children, individuals who have a low food intake or individuals consuming milk (in all cases evidence exists for increased barium absorption); (b) individuals with cardiovascular disease or hypertension (barium produces hypertension in animals); and (c) individuals suffering from nervous or muscular disorders (barium interferes with nerve transmission and muscle function). Naturally, populations exposed to high natural levels of barium in drinking water are also likely to be at greater risk.

II. PHYSICAL AND CHEMICAL PROPERTIES

A. Physical and Chemical Properties

The element barium is a silver-white metal that is highly reactive and occurs in nature only in a combined state. Its compounds occur in small but widely distributed amounts in the earth's crust. Barium is the heaviest of the stable alkaline earth metals, and it has seven naturally occurring isotopes. The free element oxidizes readily in moist air and reacts with water or with dilute acids. Pure barium has a melting point of 729°C and a boiling point of 1,640°C. It is relatively volatile and may be readily distilled (Kunesh 1978).

Barium occurs chiefly in nature as the mineral barite ($BaSO_4$) and in much smaller amounts as witherite ($BaCO_3$). The mineral forms are relatively insoluble in water, have high melting and boiling points and have very low vapor pressures (Preisman 1964).

Barium is divalent and combines readily with oxygen, nitrogen, hydrogen, ammonia, water, halogens and sulfides, generating large amounts of heat (Pidgeon 1964). Barium compounds are similar in properties to compounds of other alkaline earth metals. Substitution of barium for strontium and potassium ions is common (Kirkpatrick 1978). Barium acetate, nitrate, chloride and hydroxide are quite soluble in water, whereas barium carbonate, sulfate and fluoride are insoluble. The solubility of barium compounds increases as the pH is decreased. All of the barium salts are soluble in dilute acids except barium sulfate ($BaSO_4$) (Preisman 1964). In aqueous solution, barium is present as an ion, Ba^{+2} (Kirkpatrick 1978).

Barium sulfate is the principal form in which barium is found in nature. It is a colorless crystalline solid with a specific gravity of 4.50. It is practically insoluble in water (2.85 mg/L) but can be dissolved in concentrated sulfuric acid (Kirkpatrick 1978).

Barium carbonate is a fine white powder with a specific gravity of 4.25 and very low solubility. It melts at 811°C and has a boiling point of 1,450°C (Perry and Chilton 1973). Barium carbonate is a convenient raw material for producing other barium compounds (Kirkpatrick 1978).

Barium sulfide (BaS) is a colorless crystalline solid with a specific gravity of 4.25. It is readily soluble in water and hydrolyzes to form barium hydroxide and barium hydrosulfide. Black ash, which is a grey to black substance containing BaS, $BaCO_3$ and $BaSO_4$, is a major starting point in the manufacture of other barium compounds (Preisman 1964).

Barium chloride is a fine white crystalline material with a specific gravity of 3.856 in its anhydrous form and 3.097 in its hydrated form. The anhydrous form has a melting point of 960°C and a boiling point of 1,560°C. It forms lower-melting-point eutectics with other alkali chlorides. Its solubility in water is high. The anhydrous form absorbs water avidly (Preisman 1964).

Barium hydroxide octahydrate ($Ba(OH)_2 \cdot 8H_2O$) is a white crystalline material with a specific gravity of 2.18. It melts at 77.9°C and has a vapor pressure of 227 mm Hg at this temperature. It is also highly soluble in hot water (Kirkpatrick 1978). Less hydrated forms with three to seven waters of hydration have lower vapor pressures. The anhydrous form has a vapor pressure of 0.0 mm Hg at 150°C (Preisman 1964).

Table II-1 summarizes the properties of most of the commercially important barium compounds.

B. Manufacture and Uses

In 1977, the total U.S. consumption of barite ore was 1,508,000 tons. Nevada produces 76% of all barite mined in the U.S. The main use of barite is for drilling mud, which consumes 90% of all the barite mined (Kirkpatrick 1978).

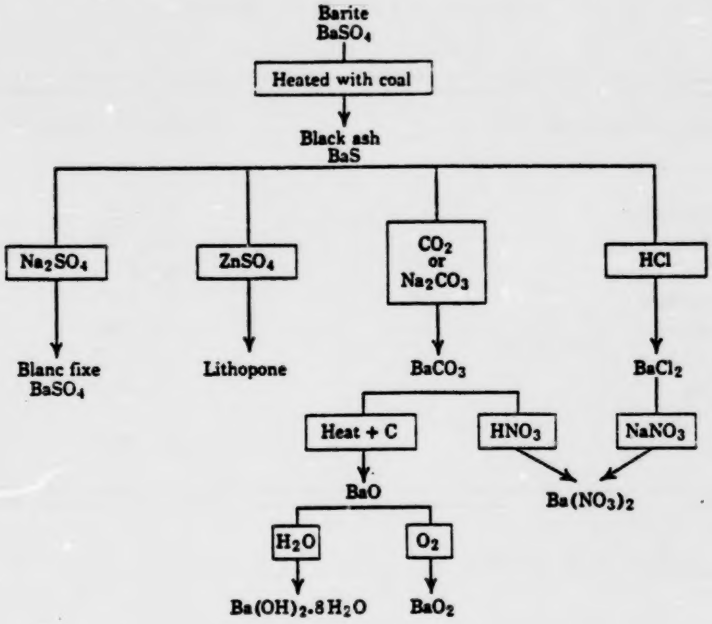
All barium compounds except precipitated $BaSO_4$ are manufactured commercially from barite ore. Barite is reduced at high temperature to water-soluble BaS; this is the chemical intermediate for other commercially produced barium compounds. Figure II-1 shows the relationship of barium compounds to the raw material.

Production rates of barium compounds in the U.S. are regarded as trade secrets. A survey done for the EPA estimated quantities of various barium compounds produced in the U.S. in 1972 (Kirkpatrick 1978). This information is summarized in Table II-2.

Table II-1 Selected Barium Compounds and Properties

Substance	Formula	Color	Melting Point (°C)	Boiling Point (°C)	Density (g/cm^3 @20°C)	Solubility in Water (parts/100 parts water)	Vapor Pressure (mm Hg)
Barium	Ba	silver metal	729-730	1637-1638	3.6	reacts	1810x10^{-5} (750°K)
Minerals							
Witherite	$BaCO_3$	yellow-white	--	1300 decomposes	4.3	0.0022	--
Barite	$BaSO_4$	red-yellow-green-grey	--	--	4.3-4.6	0.000285 (30°C)	--
Ionic Barium Compounds							
Barium Sulfide	BaS	colorless	--	--	4.25	readily soluble	--
Barium Chloride	$BaCl_2$	white	960	1560	3.856	31 (0°C)	--
Barium Oxide	BaO	colorless	1923	2000	5.32-5.72	1.5 (0°C)	--
Barium Hydroxide	$Ba(OH)_2 \cdot 8\ H_2O$	white	77.9	800 decomposes	2.18	3.89 (20°C)	227 (77.9°C)
Barium Carbonate	$BaCO_3$	white	811	1450	4.25	0.0022	760 (1297°C)
Barium Bromide	$BaBr_2$	white	847	decomposes	4.781	98 (0°C)	--
Barium Nitrate	$Ba(NO_3)_2$	colorless	592	decomposes	3.24	9.2 (20°C)	--
Barium Nitrite	$Ba(NO_2)_2$	yellowish	115	--	3.173	63 (20°C)	--
Barium Sulfate	$BaSO_4$	colorless	1580	--	4.50	0.000285 (30°C)	--
Barium Sulfite	$BaSO_3$	colorless	--	--	--	0.0197 (20°C)	--
Barium Titanate	$BaTiO_3$	light grey	1625	--	6.017	insoluble	--
Barium Fluoride	BaF_2	white	1355	--	4.89	--	--
Barium Acetate	$Ba(C_2H_3O_2)_2$	colorless	--	--	2.47	77 (26°C)	--

Adapted from Pidgeon 1964, Preisman 1964, Kirkpatrick 1978, Miner 1969, Reeves 1979, and Perry and Chilton 1973.


Barite
$BaSO_4$
Heated with coal
Black ash
BaS
Na_2SO_4
$ZnSO_4$
CO_2 or Na_2CO_3
HCl
Blanc fixe
$BaSO_4$
Lithopone
$BaCO_3$
$BaCl_2$
Heat + C
HNO_3
$NaNO_3$
BaO
$Ba(NO_3)_2$
H_2O
O_2
$Ba(OH)_2 \cdot 8H_2O$
BaO_2

Adapted from Preisman (1964).

Figure II-1 Relationship of Barium Compounds to the Raw Material

Table II-2 Estimated 1972 United States Production of Various Barium Compounds

Barium Compound	Product (tons)
Barite ore	96,000
Sulfide	73,000
Carbonate	42,000
Hydroxide	12,000
Chloride	9,000
Sulfate	5,000
Others	4,500
Total	241,500

Adapted from Kirkpatrick (1978).

Barium sulfide is the largest-volume barium compound manufactured (Kirkpatrick 1978). It is made by reaction of barite ore with carbon or coal. It is the main starting material in the production of all other barium compounds. Almost all of the BaS produced is consumed in-plant for producing other barium compounds (Kirkpatrick 1978).

Barium metal is produced commercially by the reduction of barium oxide (BaO_2) with a less reactive, non-volatile material, usually aluminum. The largest end use of barium is as a "getter" to remove the last traces of gases from vacuum and television picture tubes. It is also used to improve performance of lead alloy grids of acid batteries, as a component of grey and ductile irons, and in the manufacture of steel, copper and other metals (Kunesh 1978).

Precipitated $BaSO_4$ prepared using sodium sulfate is known as blanc fixe. It is used as a pigment, as a filler for rubber goods and as a base for lithographic inks. It is also utilized in the manufacture of photographic paper, leather and cloth (Miner 1969). When $BaSO_4$ is precipitated with zinc sulfate, it is known as lithopone. Lithopone is widely used in the manufacture of white pigment, in automobile tires and other high-grade rubber products, as a filler in rubber and plastic products, and in the production of printers' ink and cosmetics. An important medical use is as an opaque contrast medium in X-ray examination of the gastrointestinal tract (Miner 1969).

Barium carbonate serves as a raw material from which other barium compounds are produced. It is produced from BaS solution either by reaction with sodium carbonate or by reaction with carbon dioxide and water. Hydrogen sulfide is produced as a by-product in the latter reaction and slightly different product characteristics are obtained from the two processes (Kirkpatrick 1978).

Barium carbonate is used in the brick, ceramic, oil-well drilling, photographic, glass and chemical industries. Its largest use is in the brick industry where it is mixed with the wet clay to immobilize calcium and magnesium sulfates in order to obtain uniform red bricks (Kirkpatrick 1978). In the glass industry, it is added to the furnace glass. In the manufacture of television picture tubes, $BaCO_3$ is added to contain high-intensity radiation within the tube and thus reduce the hazard to viewers. In the manufacture of optical glass, it is added to the glass to obtain a high refractive index. In the ceramic industry, $BaCO_3$ is used as a fluxing ingredient in enamels, glasses and ceramic bodies (Preisman 1964).

Barium chloride is manufactured from $BaSO_4$ and hydrochloric acid. It is used as a raw material in making barium colors, as an ingredient in case-hardening and heat-treating baths and as a flux in the manufacture of magnesium metal. It is also used in manufacturing organic pigments, including Lithol Red and Red Lake. Production of $BaCl_2$ was estimated at 9,000 tons per year in 1972 (Kirkpatrick 1978).

Barium hydroxide is produced from BaO_2 and water. Production was estimated to be 12,000 tons per year in 1972. Barium hydroxide is used in lubricating oils and greases and as a component of detergents in motor oils.

It is also used in plastics stabilizers, papermaking additives, sealing compounds, vulcanization accelerators, pigment dispersants and self-extinguishing polyurethane foams and to protect limestone objects from deterioration (Kirkpatrick 1978).

Barium nitrate ($Ba(NO_3)_2$) is produced from $BaCl_2$ or $BaCO_3$. It is used in pyrotechnics, green flares, tracer bullets, primers and detonators. Production of this material was 11,000 tons in 1944 but has since decreased to the level of a minor chemical (Kirkpatrick 1978).

Barium oxide is produced from $BaCO_3$ and carbon. It is not currently manufactured in the U.S. All supplies of barium oxide are imported. Its main use has been in lubricating oils and detergents (Kirkpatrick 1978).

Barium titanate is produced by reacting barium carbonate and titanium dioxide. Its use is mainly in sonar equipment, phonograph cartridges, capacitors and other electronic equipment (Kirkpatrick 1978).

Barium silicates are formed from barium carbonate, oxide or sulfate by heating with silica to a white heat. Monobarium silicate ($BaSiO_3$) and tribarium silicate (Ba_3SiO_5) are two silicates formed. These materials are used in beet sugar refining to recover sugar from residual molasses. This process was widely used in the early 1920s and is reportedly still used by one major U.S. sugar producer (Kirkpatrick 1978).

C. Environmental Distribution

Barium is widespread in the environment. The principal mineral form is barite which is found in beds or masses of limestone, dolomite, shale and other sedimentary formations. Barium is also present in igneous rocks and coal. Barium is emitted into the atmosphere mainly by the industrial processes involved in the mining, refining and production of barium and barium-based chemicals and as a result of combustion of coal and oil (Miner 1969). The five main barium chemicals are manufactured at only seven scattered locations in the U.S.; consequently, there is no concentration of the industrial emissions of barium (Reznik and Toy 1978).

Plants have been shown to accumulate barium from the soil. Thus, food is typically the primary source of barium exposure for the general population (Reeves 1979). Generally, the ratio of barium to calcium content in food (apparently on a weight basis) is between $1:10^2$ and $1:10^5$ (Reeves 1979). Although it is possible that calcium may have an effect on the absorption of barium, no studies investigating this were located in the literature.

Barium is also present in seawater, fresh water and municipal waters. The Illinois Environmental Protection Agency has identified 16 cities and 3 sub-divisions in Northern Illinois that have drinking water sources containing 1.1 to 10.0 mg/L barium (Calabrese 1977). These affected water supplies are from deep rock and drift wells.

D. Summary

Barium is widespread in the environment. It is highly reactive and occurs in nature primarily as $BaSO_4$ and in much smaller amounts as $BaCO_3$. These mineral forms of barium are relatively insoluble in water. The main uses of barium compounds are as pigments, as fillers for rubber goods, in photographic paper, as an X-ray contrast medium, in brick and ceramic products, in oil and gas well drilling muds, in the glass industry, as plastics stabilizers, and in railroad flares, fireworks, lubricating oil additives, permanent magnets, sugar refining and steel hardening.

Barium is emitted into the atmosphere mainly from industrial processes involved in mining and production of barium chemicals and as a result of combustion of coal and oil. Barium is also found in rocks, soils, seawater, fresh water, municipal waters of the U.S. and many edible crops. Food usually represents the primary route of exposure for the general population.

III. TOXICOKINETICS

This section is divided into five parts: absorption, distribution, excretion, metabolism, and bioaccumulation and retention of barium. The majority of the pharmacokinetic studies present data generated by the use of radioactive isotope tracer techniques. By definition, the amount of radioactive barium administered in these studies is a tracer quantity and barium dosage is not described in mg/kg. However, when appropriate, a mg/kg barium dose is included in the text.

A. Absorption

Cuddihy and Ozog (1973) examined the absorption of $^{133}BaCl_2$ after direct deposition on nasal membranes or intragastric administration to one-year-old ARS/Sprague-Dawley Syrian hamsters of unspecified sex (five animals with and five without stomach ligation). Food was withheld for 12 hours prior to the administration of 0.5 mL of a solution containing a tracer quantity of $^{133}BaCl_2$. Total body radioactivity was determined immediately after isotope administration and again after four hours, when the animals were sacrificed. Gastric absorption was determined by dividing carcass radioactivity of the intragastrically intubated animals by total body radioactivity or carcass radioactivity of animals injected intravenously.

Animals with and without gastric ligation absorbed 32±17% and 11±13%, respectively, of the administered dose after four hours. However, these data should not be taken as an indication that normal gastric absorption was higher than intestinal absorption. The authors noted that intestinal absorption may not have been completed in four hours, and that there is a tendency for hamsters with stomach ligations and intragastric intubation to regurgitate some of the administered radioactive material. Nasal absorption was 61±10% of the administered dose. The authors emphasized that direct absorption from nasal tissues may represent a significant proportion of total absorption during inhalation exposure to aerosols (where nasal deposition predominates).

Young male CBL-Wistar albino rats (130 to 160 g) were given $BaSO_4$ intragastrically 16 hours after food was withdrawn (Boyd and Abel 1966). Total doses of 188, 225, 263, 300, 338 and 375 g/kg $BaSO_4$ were administered in a 150% (w/v) suspension. Clinical measurements were made for 3 to 14 days, or until death occurred. The interval to death decreased with increasing barium dosage. However, the apparent cause of death was not absorption of $BaSO_4$ from the GI tract, but stomach rupture. Although the percentage of $BaSO_4$ absorbed was not determined, the appearance of clinical signs of barium toxicity in survivors without stomach rupture indicates that some absorption of $BaSO_4$ occurred in the GI tract.

Lengemann (1959) examined the influence of lactose and lysine on the absorption of barium and other alkaline earth metals in albino Yale-Wistar rats (six females per group, 100 to 150 g). Animals were fasted for 24 hours prior to and following $^{133}BaCl_2$ administration; the animals were sacrificed 24 hours after administration. Femurs were removed and their radioactivity was counted to determine absorption. Control animals absorbed 2.66±0.29% of the administered dose. One millimole of lactose or lysine increased barium absorption significantly ($P<0.05$) to 8.52±0.75% and 10.34±0.52% of the administered dose, representing approximately three and four times the control absorption, respectively. A significant ($P<0.05$) enhancememt of absorption was also seen for calcium, magnesium, strontium and radium with lactose and for all but magnesium with lysine.

McCauley and Washington (1983) examined the influence of the specific barium salt anion on barium absorption in male Sprague-Dawley rats (250 to 300 g). Animals were fed a low-barium diet (<1 mg/day) for at least one month prior to administration of 10.0 mg ^{131}Ba/L (pH 7.0) at 0.5 mL/100 g body weight (0.05 mg barium/kg) by intubation. Administration solutions were prepared by dissolving ^{131}BaO in 6 N HCl, diluting with distilled water, and neutralizing with NaOH for the $BaCl_2$ salt or Na_2CO_3 for the $BaCO_3$ salt. The $BaSO_4$ salt was prepared by dissolving ^{131}BaO in concentrated H_2SO_4, diluting with distilled water, and neutralizing with NaOH. The authors noted the appearance of a white precipitate upon dilution of the $BaSO_4$ salt solution and indicated that the solutions were therefore shaken immediately before administration. Fasted (24 hours) animals were given $^{131}BaCl_2$ and then sacrificed at 2, 15, 30, 60, 120 and 480 minutes after administration. *Ad libitum* fed rats received either $BaCl_2$, $BaCO_3$ or $BaSO_4$ and were sacrificed at 2, 5, 10, 20, 30, 60 and 120 minutes and 24 hours after administration. Blood and eye samples were obtained from all animals for determination of ^{131}Ba content.

The 24-hour fasted rats had the highest blood ^{131}Ba concentration, which peaked 15 minutes after dosing. The blood ^{131}Ba concentration of fed rats was lower and peaked later (60 minutes post-administration). In fed rats, the

$BaCO_3$ and $BaSO_4$ groups had peak blood concentrations of ^{131}Ba that were approximately 45% and 85%, respectively, of the $BaCl_2$ group. It is interesting to note the relatively high blood concentration of ^{131}Ba after administration of $BaSO_4$, a relatively insoluble compound at pH 7.0 (as indicated by the presence of the precipitate in the solution). These results appear to indicate that even $BaSO_4$ may be relatively easily absorbed from the GI tract.

Comparative studies of the effects of age and fasting on absorption of barium (^{140}Ba), calcium (^{45}Ca), radium (^{226}Ra) and strontium (^{85}Sr) from the GI tract in female brown-hooded August strain rats (14 days to 20 weeks of age) were performed by Taylor et al. (1962), using radioactive tracer techniques. The radioisotopes were administered as a single dose by intragastric intubation, and the animals were sacrificed approximately seven hours later. Absorption was calculated to be the sum of radioactivity remaining in the carcass and urine less that present in the GI tract (Table III-1). The amount of barium absorbed decreased from about 85% in the very young animal (14 to 18 days) to less than 10% in the adult animal (60 to 70 weeks). The extent to which the high absorption in the youngest group resulted from (1) a diet of maternal milk instead of solid foods, (2) an increased requirement for calcium or (3) a lack of development of mechanisms controlling the absorption of metals from the GI tract was not determined. The authors did note that when cow's milk replaced the 0.01 N HCl in the solution administered to six-to-eight-week-old rats, there was no difference in barium absorption. The absorption rate significantly increased ($P<0.01$) from 6.8% to 20.0% in the six-to-eight-week-old animals deprived of food, but not water, for 18 hours

Table III-1 Absorption of Alkaline Earth Metals after Intragastric Administration[a]

Subject	Age	Ca	Sr	Ra	Ba
Fed Rats	14-18 days	97.5±0.8 (9)	95.2±0.4 (31)	78.6±3.1 (12)	84.6±2.4 (10)
	22 days	-	74.4±2.4 (5)	-	63.0±4.1 (5)
	6-8 weeks	63.0±2.6 (15)	24.6±1.0 (45)	11.3±1.5 (20)	6.8±0.3 (5)
	60-70 weeks	31.6±2.0 (10)	11.1±0.8 (24)	3.2±0.7 (4)	7.5±1.9 (10)
Fasted Rats	6-8 weeks	53.7±2.4 (5)	24.2±2.4 (19)	17.5±2.6 (9)	20.0±2.7 (5)
	60-70 weeks	24.8±1.9 (10)	16.7±1.8 (18)	8.4±1.3 (3)	19.9±6.8 (5)

[a] Results expressed as percentage of administered dose ± standard error of the mean, with the number of animals used in parentheses.

Adapted from Taylor et al. (1962).

prior to administration. Another series of experiments, in which animals (6 to 8 weeks or 60 to 70 weeks old) received oral administration of ^{45}Ca, ^{85}Sr, ^{140}Ba or ^{226}Ra, followed immediately by oral administration of 300 µg of SO_4^{-2}, indicated that the percentage of absorption in fed and fasted animals did not significantly differ from the results given in Table III-1.

Clary and Tardiff (1974) published data in abstract form after examining the absorption and distribution of a single oral dose (1, 5, 25 or 125 mg/kg) of $^{133}BaCl_2$ in male weanling rats (weight and strain not specified). The animals were sacrificed at 0.5, 2, 4, 8, 16 and 24 hours after exposure, and tissue ^{133}Ba concentrations were measured (values were not presented in the abstract). The authors noted that the results indicated that ^{133}Ba is rapidly absorbed from the GI tract. Peak ^{133}Ba concentrations occurred 30 minutes post-administration in blood and soft tissues and two hours post-administration in the femur. Clary and Tardiff (1974, p. 139) stated that: "Total uptake of Ba increased with increasing dosage; however, relative uptake was inversely related to the dosage."

Cuddihy and Griffith (1972) administered by gavage 5 mL of a solution containing 3.7 mg $^{133}BaCl_2$ (0.28 and 0.53 mg/kg) to two beagle dogs (13 and 7 kg, 2 and 4 years of age, respectively). Mathematical treatment of total body retention and excretion data yielded an estimated GI absorption of 7% for barium.

The barium GI absorption factor (f_1) has not been experimentally determined in humans. This is evident by the absence of data in the report of the 1973 International Commission on Radiological Protection, Publication 20, entitled "Alkaline Earth Metabolism in Adult Man" (ICRP 1973). Tipton et al. (1969) and the National Academy of Sciences (NAS 1982) reported that in 1960 the ICRP estimated an f_1 value for ingested barium in man of 5%. Tipton et al. (1969) reported in a long-term balance study of 22 elements (see Section III.E., Bioaccumulation and Retention, for details) that the ICRP values for f_1 appear to be valid for those elements excreted almost entirely in the urine. Data presented in Section III.D., Excretion, indicate that the primary route of barium excretion in man and animals is fecal. The ICRP value for f_1 may be low because it does not take into account the reexcretion of absorbed barium into the gut. Harrison et al. (1967) suggested that the absorption and excretion of ^{133}Ba and ^{223}Ra are similar in man, indicating that the f_1 for barium may be closer to that of radium at 10%.

Beagle dogs (male and female, 8 to 14 kg, 15 to 24 months of age) were utilized in $BaCl_2$ inhalation studies (Cuddihy and Griffith 1972). Aerosols were generated from solutions containing 3.7 mg $BaCl_2$/mL, 6.3 mg lanthanum chloride ($LaCl_3$)/mL and tracer amounts of ^{140}Ba and ^{140}La. The concentration of barium in the resulting aerosol was not indicated. One day after inhalation exposure, the tissue content of ^{140}Ba revealed that about 75% of the barium had been absorbed into the general circulation.

Cuddihy et al. (1974) extended their observations of barium absorption in beagle dogs (sex and age not indicated) using various barium salts containing ^{133}Ba. The authors indicated the barium concentration in the solutions generating the aerosols, but not the final concentration of barium in the breathing chamber. Groups of three dogs each inhaled $BaCl_2$, $BaSO_4$, heat-treated $BaSO_4$, and barium fused in montmorillonite clay in the form of aerosols having activity median aerodynamic diameters of about 2.3 μm, 1.0 μm, 0.9 μm and 2.2 μm, respectively. Dogs were sacrificed on the sixteenth day after inhalation. An additional group that inhaled the fused clay aerosol was sacrificed on day 512. The radioactivity distribution was determined by whole-body linear profile scans; urinary and fecal excretions were collected and their radioactivity counted. These same compounds were cleared from the lungs in proportion to their aqueous solubilities and the specific surface area of the inhaled particle. The initial lung body burden decreased by 50% (half-time of clearance) for these compounds at approximately 1 hour, 2 days, 5 days and over 400 days for $BaCl_2$, $BaSO_4$, heat-treated $BaSO_4$, and barium fused to clay, respectively.

Measurements of the clearance of tracer levels of $^{131}BaSO_4$ (estimated maximum initial burden of 90 μg or 0.09 mg/kg from a 30- to 90-minute exposure) from the respiratory tract of female beagle dogs (10±1 kg) were performed by Morrow et al. (1964). The biological half-life was eight days.

Spritzer and Watson (1964) examined lung absorption and ciliary clearance of 0.15 cm^3 of a $BaSO_4$ particle suspension containing 100 μg of $^{133}BaSO_4$ per 0.5 cm^3 (0.073 to 0.086 mg $BaSO_4$/kg). After intratracheal administration in male Wistar rats (350 to 410 g), 15% of the initial lung burden was cleared in 24 hours. "Lung-to-blood" transfer mechanisms accounted for 48% of this clearance while the remainder occurred via ciliary action. The authors noted that these data suggest that a fair degree of solubilization of $BaSO_4$ occurs in vivo.

Research comparing the distribution of calcium and barium is discussed in the following section, III. B., Distribution. The mode of administration in these experiments bypasses absorption from the GI tract. Therefore, these studies provide no evidence to indicate what effect calcium may have on barium absorption. No specific references providing information on this were located in the literature.

B. Distribution

McCauley and Washington (1983) examined the distribution of ^{131}Ba administered intragastrically as the chloride, the carbonate or the sulfate salt. Fed or 24-hour fasted male Sprague-Dawley rats (250 to 300 g) were given 10 mg $^{131}Ba/L$ at 0.5 mL/100 g body weight (0.05 mg/kg). Eye and blood samples were obtained from fasted rats at 2, 15, 30, 60, 120 and 480 minutes after administration and from fed rats at 2, 5, 10, 20, 30, 60 and 120 minutes and 24 hours. In addition, the heart, one lobe of the liver, both kidneys and the rostral thigh muscle were removed from the fed rats that had received $BaCl_2$ for 24 hours. The highest rate of ^{131}Ba accumulation in the eyes was seen in animals that had received the chloride salt and had been fasted for 24 hours prior to barium administration. A lower rate of accumulation was seen with the fed animals, and concentrations of ^{131}Ba in the eyes were nearly identical for the chloride and sulfate barium salts the first hour after dosing. Rats given $^{131}BaCO_3$ accumulated ^{131}Ba at approximately one-half the rate of rats given $BaCl_2$ or $BaSO_4$ for similar time periods. During the second hour, the $^{131}BaCl_2$ content of the eye increased to almost three times the blood ^{131}Ba concentration; it remained constant for the 24-hour sampling period. Of the tissues obtained at 24 hours after administration, the eye, kidney and skeletal muscle were nearly equivalent in ^{131}Ba content, the liver had a lower concentration than blood and the heart had accumulated approximately three times more ^{131}Ba than the eye.

Dencker et al. (1976) reported the localization of $^{133}BaCl_2$ in pigmented (CBA) and albino (NMRI) mice. Males (25 to 30 g) and late-gestation females (40 g) were sacrificed after intravenous injection of 63 μg barium/kg (0.063 mg barium/kg) containing $^{133}BaCl_2$. The calcified tissues, cartilage, kidney and melanin-containing tissues of the male and female pigmented animals had the highest ^{133}Ba activity at the earliest observation time (20 minutes after administration), but albino mice did not have correspondingly high activity in eyes or hair follicles. The calcified and cartilage tissues retained activity even at the longest survival time, 32 days.

High concentrations of activity in the epiphysial regions and surface areas of bone were seen initially, followed by predominance in the diaphysial areas. Skull bones had initially high activity which was not retained as long as that in the long bones. After four days the only sites other than bone, cartilage and melanin-containing tissue having ^{133}Ba activity were the GI contents, urinary tract and salivary gland.

In the same study, 18-day fetuses of pigmented mice were sacrificed at 1, 4 and 24 hours after administration, and of albino mice at 1 and 48 hours after administration. At one hour, uptake predominated in skeletal growth zones and the eyes. More uptake in the skeleton, eye and other soft tissue was seen at four hours. The activity levels decreased at 24 and 48 hours, leaving activity only in the skeleton at 48 hours. At each time point, fetal activity was considerably lower than maternal activity. Since measurements were made by autoradiography and impulse counting techniques, this study was only qualitative in nature.

Bligh and Taylor (1963) examined the distribution of $BaCl_2$ and strontium chloride ($SrCl_2$) in brown-hooded August rats (female) of two age groups (6 to 8 weeks or 13 to 15 months, weight not specified) after a single intravenous injection of a tracer quantity of ^{140}Ba and ^{85}Sr. Tissue activities of ^{140}Ba at various time intervals after injection are listed in Table III-2. The highest activity in soft tissues occurred at the first time point (ten minutes), and fell roughly parallel with the blood serum activity. Analysis of tissue calcium content revealed that ^{140}Ba uptake was generally in proportion to the calcium content of the tissue. One exception was the submaxillary gland, where the specific activity did rise above that of the blood serum. Older animals had approximately twice the barium activity of the young animals in both lungs and submaxillary glands.

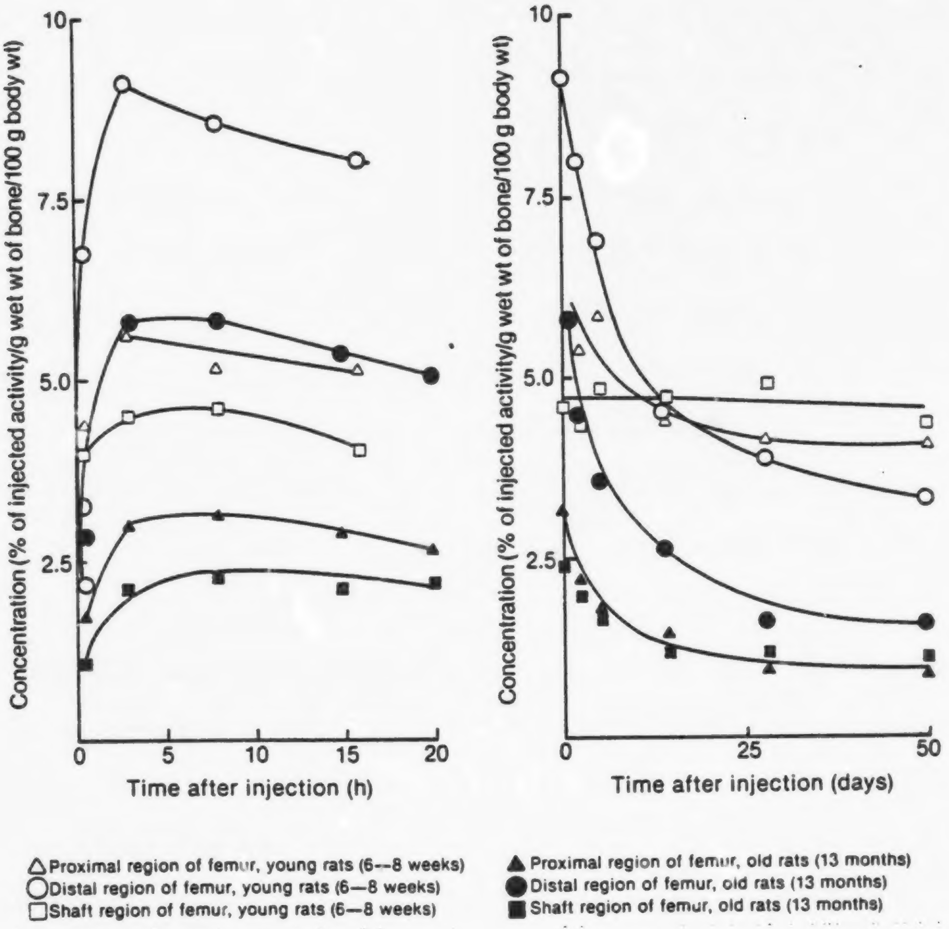
The concentrations of barium in the proximal, distal and shaft regions of the rat femur were also determined in the study by Bligh and Taylor (1963), and are shown in Figure III-1. The distal region contained the most active areas of bone growth and the highest concentration of ^{140}Ba in the femur. The activities in all three areas of bone were always higher in the younger animals than in the older animals. During the 50 days post-injection, ^{140}Ba

Table III-2 Tissue Activities of ^{140}Ba in Young (6 to 8 weeks) and Old (13 months) Rats[a]

Time After Injection	Muscle		Liver		Lungs		Submaxillary Gland		Blood Serum	
	Young	Old	Young	Old	Young	Old	Young	Old	Young	Old
10 min	0.40	0.36	0.44	0.68	1.09	2.08	1.44	3.35	2.00	NA[b]
30 min	0.20	0.28	0.23	0.48	0.53	1.09	1.62	2.23	0.67	NA[b]
3 hr	0.08	0.16	0.025	0.13	0.085	0.55	0.44	2.04	0.073	NA[b]
8 hr	0.031	0.058	0.014	0.058	0.054	0.23	0.51	0.89	0.036	0.13
20 hr	NA[b]	0.012	0.005	0.027	0.038	0.10	0.14	0.59	0.12	NA[b]
5 days	NA[b]	0.0012	0.004	0.007	0.013	0.050	0.022	0.12	0.0043	0.0096

[a] Results expressed as % injected dose/g wet weight/100 g body weight.
[b] Not available.

Adapted from Bligh and Taylor (1963).



Adapted from Bligh and Taylor (1963).

Figure III-1 Concentration of ^{140}Ba in the proximal, distal and shaft regions of the rat femur as a function of time after injection.

activity decreased primarily in the distal region in the younger animals and in all three regions in the older animals.

In the same study, the concentration of ^{140}Ba in the incisor and molar teeth was also examined up to 80 days post-administration. The data indicated that the uptake of ^{140}Ba in molar teeth was similar in old and young animals (peak concentrations at eight hours of 5.57% and 6.22% of injected activity/g wet weight/100 g body weight), but that the removal was more rapid in the older animals. Incisor uptake of ^{140}Ba in older rats was about twice that in the young rats from eight hours after injection (11.70% versus 7.40% of injected activity/g wet weight/100 g body weight) until 50 days (5.84% versus 2.27% of injected activity/g wet weight/100 g body weight). The concentration of ^{140}Ba in incisor teeth was maximal at five days in both old and young animals. These values were 17.17% and 9.60% of injected activity/g wet weight/100 g body weight, respectively.

The skeletal distribution of a single intravenous dose of tracer amounts of high-specific-activity ^{133}Ba, ^{45}Ca or both radioisotopes was measured in three 10-year-old beagle littermates (sex unspecified) by Ellsasser et al. (1969). One animal was injected with 2.08 millicuries of ^{45}Ca/kg body weight. The second was injected with 0.32 millicuries of ^{133}Ba/kg. The third received a double tracer injection of ^{45}Ca and ^{133}Ba (0.42 millicuries/kg and 0.31 millicuries/kg, respectively). Blood samples and excretions were collected. On day seven post-administration, the animals were sacrificed and the skeleton was dissected. The skeletal radioactivity was assayed by liquid scintillation counting and autoradiography. The skeletal distribution (shown in Table III-3)

Table III-3 Distribution of ^{133}Ba and ^{45}Ca Radioactivity in the Dog Skeleton[a]

Skeletal Location	Dog 1 ^{45}Ca	Dog 2 ^{133}Ba	Dog 3 ^{45}Ca	Dog 3 ^{133}Ba	$\bar{x} \pm SE$[b]
All vertebrae	1.38	1.58	1.46	1.53	1.49±0.04
Ribs	1.26	1.41	1.48	1.57	1.43±0.07
Sternum	3.26	3.89	3.71	3.98	3.71±0.16
Skull	0.76	0.67	0.67	0.65	0.69±0.03
Mandible	0.90	0.74	0.54	0.50	0.67±0.09
Scapula	0.89	0.94	0.87	0.92	0.91±0.02
Innominate	1.09	1.18	1.29	1.22	1.20±0.04
Humerus	1.12	1.08	1.13	1.10	1.11±0.01
Femur	1.09	0.97	0.99	0.99	1.01±0.03
Femur, proximal epiphysis	1.02	1.38	1.30	1.39	1.27±0.09
Femur, mid-shaft	0.60	0.46	0.51	0.50	0.52±0.03
Femur, distal epiphysis	1.48	1.59	1.19	1.26	1.38±0.09
Radius	0.60	0.57	0.50	0.49	0.54±0.03
Ulna	0.60	0.57	0.58	0.61	0.59±0.01
Tibia-fibula	0.81	0.61	0.61	0.61	0.66±0.05
Forefoot	0.48	0.74	0.50	0.63	0.59±0.06
Hindfoot	0.48	0.63	0.50	0.59	0.55±0.04

[a] Results expressed as the ratio of local bone specific activity to whole body specific activity.

[b] Mean ± standard error of the mean.

Adapted from Ellsasser et al. (1969).

was about the same for ^{133}Ba and ^{45}Ca, and the specific activities of the trabecular bones were higher than those of the cortical bones. The skull, mandible, radius, ulna, tibia-fibula and mid-shaft of the femur had specific activities less than the whole-body specific activity. When the long-term rate of transfer from blood to bone was measured at day five, ^{133}Ba transfer was found to be 2 to 3.5 times larger than calcium transfer. The autoradiographs revealed that this preferential uptake of barium was localized on bone surfaces.

The distribution of ^{140}Ba and ^{45}Ca injected intraperitoneally was examined in two-month-old rats of both sexes (unspecified strain or weight) over a 48-hour period (Bauer et al. 1956). Peak plasma activities of ^{140}Ba and ^{45}Ca (14.4% and 11.4% of the dose/mg of calcium, respectively) occurred at the first time point examined (15 minutes after administration). Plasma ^{140}Ba concentrations were lower than ^{45}Ca concentrations after the first half hour.

From 15 minutes to 48 hours post-administration the concentration of ^{140}Ba in incisor teeth increased from 0.49% to 1.36% of the dose. The ^{140}Ba content of the tibial ends and shafts increased up to 24 hours post-injection (2.35% to 4.30% of dose and 0.15% to 0.93% of dose, respectively). At 48 hours the ^{140}Ba concentration decreased to 3.85% of the dose in the tibial ends but remained at 0.93% of the dose in the tibial shafts.

The distribution of radioactive tracer amounts of barium, calcium, radium and strontium was determined after intravenous administration into a healthy 60-year-old male (80 kg) (Harrison et al. 1967). The plasma concentrations of radioactivity are listed in Table III-4. Plasma concentrations as a function of time for ^{223}Ra and ^{133}Ba were very similar, as were those of ^{85}Sr and ^{47}Ca. At ten minutes post-administration, the barium concentration in plasma was only about 7% of the initial dose; it was undetectable after seven days (169 hours). The calculated ^{133}Ba distribution in the extracellular fluid (E.C.F.) and tissue (including the skeleton) are shown in Table III-5. When the authors plotted the tissue content against time after injection, the maximum tissue content of ^{133}Ba (55%) was determined to occur at 1.5 hours after injection when the E.C.F. content was about 24% of the initial dose. Maximum tissue concentrations for ^{47}Ca and ^{85}Sr were calculated to occur at about 20 hours after injection. Calculation of apparent transfer rates from blood to bone yielded values three to four times greater for barium than for calcium (Lloyd 1968).

Maternal and fetal tissue concentrations of barium were determined in females (16 to 39 years old) having uncomplicated single births (Creason et al. 1978). Maternal venous and cord blood, maternal pubic hair and placenta samples were obtained at birth and analyzed. Maternal hair samples from the scalp were obtained within two months of delivery. Correlations between maternal and fetal tissue barium content, as well as between tissue concentration and other factors (e.g., age, education), were attempted. The geometric mean of the ratio between umbilical cord blood and maternal blood concentrations of barium was 1:1.12 for 170 observations and was the only significant correlation ($P<0.05$) between tissues. The statistical methods used were vague and the study was poorly designed. Therefore, the only conclusion was that barium did cross the placental barrier.

Table III-4 Plasma Concentrations of ^{133}Ba, ^{223}Ra, ^{85}Sr and ^{47}Ca in a Man at Various Times After a Single Intravenous Administration[a]

Hours After Administration	^{133}Ba	^{223}Ra	^{85}Sr	^{47}Ca
0.17 (10 minutes)	6.94	3.95	6.56	6.05
3	1.15	0.975	2.79	2.80
12	0.335	0.214	1.74	1.85
25	0.119	0.135	1.25	1.40
49	0.082	0.058	0.732	1.08
74	0.035	0.031	0.497	0.845
97	0.022	0.022	0.363	0.670
145	0.012	0.011	-	-
169	Undetectable	-	0.145	0.399

[a] Results are expressed as percentage of the injected dose per liter of plasma.

Adapted from Harrison et al. (1967).

Table III-5 Calculated ^{133}Ba Distribution at Various Times After Intravenous Administration to a 60-Year-Old Male[a]

Hours After Administration	Extracellular Fluid	Tissue
0.5	44.4	45.6
1	30.3	52.7
2	19.4	53.6
5	9.4	46.6
10	5.1	40.9
24	2.2	29.0
36	1.4	25.6
48	0.9	23.0

[a] Results are expressed as percentage of the dose administered.

Adapted from Harrison et al. (1967).

C. Metabolism

Barium metabolism has been studied by comparing the rates for barium with those of strontium (Bligh and Taylor 1963) and calcium (Bauer et al. 1956, 1957, Ellsasser et al. 1969) for clearance from plasma, skeletal accretion and excretion. The experimental protocol details of these studies are presented in Section III. B., Distribution, and Section III. E., Bioaccumulation and Retention. The rates of all three processes, after intravenous administration, were higher for barium than for calcium or strontium. The authors agreed on the hypothesis that barium, perhaps by reacting with PO_4^{-3} ions, was deposited in bone (1) partly by ionic exchange with calcium, at actively calcifying surfaces, and (2) partly by the more irreversible process of surface adsorption. Bauer et al. (1956, 1957) concluded that the skeletal metabolism of barium in both humans and rats closely parallels that of calcium even though they differ quantitatively. No metabolic studies after oral administration of barium have been reported in the literature.

D. Excretion

Two pairs of mature lactating Redpoll X Ayrshire cows (weight not indicated) received tracer amounts of ^{140}Ba orally, followed by an intravenous injection one to two months later (Garner et al. 1960). Excretion in milk during the first eight days after administration was approximately 0.6% of the oral dose and 10% of the intravenous dose. Fecal and urinary excretion rates over the same period were about 98% and 1.1%, respectively, of the oral dose and 37% and 3.4% of the intravenous dose.

A comparative study of the metabolism of ^{140}Ba and ^{45}Ca was done using male and female two-month-old rats of unspecified weight (Bauer et al. 1956). Tracer quantities of ^{140}Ba were administered by intraperitoneal injection and the animals were sacrificed at intervals ranging from 15 minutes to 48 hours after injection. No urine was collected from those animals sacrificed less than four hours after administration. Fecal excretion of ^{140}Ba was greater than urinary excretion at each post-administration time interval. Twenty-four hours after administration, approximately 7% of the initial dose had been collected in the urine and 20% in the feces, compared to 1% and 6%, respectively, for calcium. Calculations of fecal excretion utilized the radioactivity present in both the feces and GI tract.

Excretion of $BaSO_4$ was monitored after female beagle dogs (10±1 kg) inhaled tracer amounts of $^{131}BaSO_4$ (maximum estimated initial burden of 90 µg/kg or 0.09 mg/kg) (Morrow et al. 1964). The urine/feces ratio of isotope excretion was 0.057 for the first 24 hours after exposure, gradually increasing to 0.650 by the seventh day. Excretions were collected for up to four weeks after exposure, but data were only presented for the first seven days.

Bauer et al. (1957) did a double radioactive tracer study to compare the metabolism of ^{140}Ba and ^{45}Ca after intramuscular injection in six children and intravenous injection in two adults (Bauer et al. 1957). Plasma, fecal and urinary samples were collected for up to six days after administration. The data were treated mathematically to determine the skeletal accretion rates, but insufficient data were presented to calculate the actual urinary and fecal excretion of barium. The authors did state that the excretion rate for ^{140}Ba was considerably higher after intravenous administration to adults than after intramuscular administration to children and that the excretion rate was higher for ^{140}Ba than for ^{45}Ca.

A healthy 60-year-old man was given ^{133}Ba in a single intravenous injection (Harrison et al. 1967). Urinary and fecal excretion in the first eight days after administration was approximately 85% of the injected dose and the ratio of total fecal to total urinary excretion was 9:1 from day 8 to day 28. Barium excretion in the saliva and seminal fluid six hours after administration was 0.22% and 0.81% of the administered dose.

An early study by Tipton et al. (1966) examined trace element intake and excretion in two subjects (35-year-old male, approximately 75 kg, and 34-year-old female, approximately 62 kg) over a 30-day period. Barium content was analyzed by emission spectroscopy and the results are shown in Table III-6.

The respective mean urinary excretion rates were about 16% and 36% of total barium intake and mean fecal excretion rates were 34% and 115% of total intake. Therefore, approximately two to three times more barium was excreted via the feces than via the urine in these individuals.

The results of a long-term study of the intake and excretion of barium and 31 other elements in two males (23 years old, 100 kg, and 25 years old, 71 kg) over a 50-week period are shown in Table III-7 (Tipton et al. 1969). From the data, the respective fecal excretion rates were about 106% and 96% of

Table III-6 Barium Mean Daily Ingestion and Excretion in Humans

	Barium, g/day (mg/day)				
Subject	Intake	Feces	Urine	Total Excreta	Balance
1	1.77×10^{-3} (1.77)	0.60×10^{-3} (0.60)	0.28×10^{-3} (0.28)	0.88×10^{-3} (0.88)	0.89
2	1.54×10^{-3} (1.54)	1.78×10^{-3} (1.78)	0.56×10^{-3} (0.56)	2.34×10^{-3} (2.34)	-0.80

Adapted from Tipton et al. (1966).

Table III-7 Barium Mean Daily Ingestion and Excretion in Humans

Subject	Barium Content (mg/day)				Balance (±95% confidence interval)
	Diet	Feces	Urine	Total Excreta	
1	0.65±0.03	0.69±0.08	0.037±0.012	0.73±0.08	-0.08±0.18
2	0.92±0.07	0.88±0.18	0.017±0.003	0.90±0.18	0.02±0.20

Adapted from Tipton et al. (1969).

total barium intake while urinary excretion rates over this period were 5.7% and 1.8%. While subject 2 consumed approximately 42% more barium (solids and liquids) during the 50-week period, the patterns of excretion and barium balance in the two were similar.

The excretion of stable urinary barium by two children (a 5.5-year-old female and a 7.5-year-old male) and four adults (three females and one male averaging 45 years of age) was measured by Sutton and Shepherd (1973). Sodium alginates were given orally for seven days to adults and for four days to children. During this period urinary barium excretion decreased to 64% of control in both age groups. Dietary barium intake was controlled for the children and estimated for the adults. The decreased barium urinary excretion was attributed to a reduction of barium absorption in the gut. The reduced absorption should have resulted in an increase in fecal excretion of barium. However, the authors noted that relatively high fecal excretion after alginate administration prevented the increased fecal excretion of barium from being seen.

E. Bioaccumulation and Retention

The accumulation of $BaCl_2$ in tissues of four-week-old Charles River rats (male and female) exposed to 0, 10, 50 or 250 ppm of barium (as $BaCl_2$) in drinking water was determined (Tardiff et al. 1980). Results of analysis of the tissues after barium exposure for 4, 8 and 13 weeks are shown in Table III-8. The calculated cumulative doses of barium were given only for the 13-week exposure group, and are shown in Table III-9. The calculated

Table III-8 Concentration of Barium in Tissues from Rats Exposed to Barium in Drinking Water[a]

Dose (ppm)	Liver	Bone	Muscle	Heart
	4 Weeks			
Females				
0	0.11±0.03(5)	8.3±0.7(5)	0.18±0.03(5)	0.22±0.05(5)
10	0.26±0.05(5)	9.6±0.9(5)	0.35±0.06(5)	0.36±0.07(5)
50	0.42±0.11(10)	50.3±4.6(10)	0.56±0.08(10)	0.56±0.09(10)
250	0.50±0.08(5)	230.2±9.9(5)	1.40±0.85(5)	0.44±0.05(5)
Males				
0	0.11±0.06(5)	8.1±0.8(5)	0.26±0.10(5)	0.26±0.12(5)
10	0.30±0.06(5)	9.6±0.05(5)	0.51±0.10(5)	0.45±0.06(5)
50	0.33±0.05(8)	65.0±5.7(5)	0.56±0.04(9)	0.58±0.12(9)
250	0.77±0.07(5)	198.4±9.5(5)	1.46±0.37(5)	0.93±0.20
	8 Weeks			
Females				
0	0.14±0.03(5)	7.3±0.05(5)	0.31±0.08(5)	0.24±0.08(5)
10	0.40±0.09(5)	12.1±1.9(5)	0.75±0.22(5)	0.64±0.18(5)
50	0.26±0.04(10)	39.2±3.4(10)	0.41±0.06(10)	0.41±0.08(10)
250	0.40±0.11(5)	229±10.4(5)	0.60±0.16(5)	0.38±0.06(5)
Males				
0	0.08±0.02(5)	7.0±0.3(5)	0.23±0.08(5)	0.15±0.04(5)
10	0.49±0.09(5)	13.3±0.1(5)	0.78±0.15(5)	0.87±0.21(5)
50	0.32±0.05(9)	38.7±4.6(9)	0.60±0.12(9)	0.47±0.09(9)
250	0.67±0.09(5)	236±9.9(5)	0.79±0.05(5)	0.98±0.19(5)
	13 Weeks			
Females				
0	0.15±0.05(5)	10.3±1.2(5)	0.22±0.07(5)	0.18±0.05(5)
10	0.35±0.04(5)	16.2±3.3(5)	0.49±0.08(5)	0.29±0.01(5)
50	0.36±0.05(10)	50.5±7.4(10)	0.70±0.14(10)	0.40±0.04(10)
250	0.38±0.07(5)	214±9.3(5)	0.48±0.09(5)	0.44±0.08(5)
Males				
0	0.12±0.05(5)	7.9±0.7(5)	0.16±0.06(5)	0.25±0.09(5)
10	0.37±0.07(5)	12.8±1.4(5)	0.46±0.07(5)	0.36±0.01(5)
50	0.36±0.04(10)	50.5±5.7(10)	0.45±0.04(10)	0,45±0.04(10)
250	0.25±0.05(5)	226±15.9(5)	0.40±0.06(5)	0.31±0.03(5)

[a] Values are reported as μg/kg ± standard error of the mean, with number of samples in parentheses.

Adapted from Tardiff et al. (1980).

Table III-9 Dosage of Barium in Rats' Drinking Water for 13-Week Exposure

ppm (mg/L)	Sex[a]	Initial[b]	Final[b]	$\bar{x}$ ± SE[c]	Cumulative at 90 days (mg/kg)
10	M	2.8	1.5	1.7±0.1	154
	F	2.7	1.9	2.1±0.1	189
50	M	12.9	6.3	8.1±0.4	732
	F	14.5	6.9	9.7±0.4	877
250	M	64.2	27.5	38.1±1.7	3433
	F	68.3	35.5	45.7±1.6	4114

[a] M = males; F = females.
[b] Units of mg/kg/day.
[c] Mean ± Standard error of the mean.

Adapted from Tardiff et al. (1980).

estimations of total barium dosages for the four- and eight-week exposure groups are given in Table III-10. Control animals contained barium in the tissues examined (liver, bone, heart and muscle), with bone having about 50 times higher concentrations than other tissues. In the experimental animals, there was no apparent sex difference in the bioaccumulation of barium in any tissue. The concentrations of barium accumulated did not appear to be proportional to the duration of exposure. However, bone accumulation of barium after exposure to concentrations of 50 and 250 ppm increased approximately 5-fold and 21- to 34-fold, respectively, when compared to controls. Insufficient data were presented to determine the body retention of barium during exposure.

Young male Hartley guinea pigs (averaging 208 g) were fed a diet *ad libitum* of 45% crown vetch containing either 12 or 27 ppm barium (dry weight) for 100 days (Young et al. 1978). (Estimated total barium dosages, calculated by assuming 1 ppm in food equals 0.040 mg/kg/day, are approximately 22 and 50 mg barium/kg, respectively.) Animals were then sacrificed and tissue contents of barium and other elements were determined. The crown vetch containing 27 ppm barium had been collected from within 3 meters of an interstate highway and represented the experimental group. Insufficient data were presented to calculate the rates or percentage of bioaccumulation and retention. However, the authors reported that some experimental guinea pig tissues contained higher levels of barium than the control. These were the kidney (8.3 versus 2.0 ppm dry weight, respectively) and bone (21.0 versus 4.5 ppm dry weight, respectively). The reported values represent 315% and 367% increases over control barium content in kidney and bone, respectively.

Table III-10 Calculated Estimations of the Total Barium Dosage for Rats from Drinking Water Exposure[a]

ppm (mg/L)	Exposure Time	
	4 weeks	8 weeks
10	75	140
50	375	700
250	1857	3500

[a] These dosages were estimated from data presented in Tardiff et al. (1980) and are expressed in units of mg/kg.

Adapted from Tardiff et al. (1980).

Sutton et al. (1972) examined the effects of sodium alginate derivatives on the retention of barium in inbred female albino rats (12 weeks old, unspecified weight). Rats (assumed to weigh approximately 100 g) ingested 10 or 740 µg barium including tracer amounts of ^{133}Ba (0.01 or 0.74 mg/kg) and either cellulose (control) or a sodium alginate derivative added to the diet over a two-day period. The amount of barium retained was expressed as the ratio of the carcass activity to the total activity recovered (urine + feces + carcass + gut contents). Controls retained 0.60% of orally administered ^{133}Ba, and sodium alginate derivatives caused a 12% to 25% lower retention when measured seven days after administration. Barium retention at day four after parenteral administration of 5 or 14 µg barium (0.05 or 0.014 mg/kg) was 5% to 12% lower in alginate-fed rats than in controls. Controls retained about 58% of the dose. The authors suggested that one mechanism of alginate action was the inhibition of barium re-absorption from the GI tract.

Wistar albino rats (either sex, eight months old, weight unspecified) were given intravenous injections of tracer amounts of ^{45}Ca and ^{85}Sr or ^{133}Ba and ^{85}Sr (Domanski et al. 1969). Blood and bone samples were collected at sacrifice from one hour to 18 days after isotope administration. Urine and feces were collected through day 16. The whole-body retention was approximately 60% of the dose for all isotopes one day after administration. However, at day 16 fractional whole-body retention of ^{133}Ba and ^{45}Ca was about 35% of the dose while that of ^{85}Sr was only about 20%. The whole-body accretion rate from ^{133}Ba data (27.2×10^{-4} g calcium/hour) was 5.6 times that from ^{45}Ca data (4.84×10^{-4}g calcium/hour). The authors noted that these data suggest a preferential incorporation of barium into bone with respect to calcium.

Bauer et al. (1956) calculated the skeletal exchangeable calcium fraction and accretion rates in two-month-old rats of both sexes after intraperitoneal administration of ^{140}Ba and ^{45}Ca. The experimental details for this study have already been discussed in Section III. B., Distribution. The size of the exchangeable skeletal calcium fraction was about the same when calculated from ^{140}Ba and ^{45}Ca data (41 and 39 mg, respectively). Calculated accretion rates were higher for ^{140}Ba than ^{45}Ca in the whole skeleton (5.2 and 2.4 mg calcium/hour, respectively), tibia ends (0.34 and 0.14 mg calcium/hour, respectively) and tibia shafts (0.064 and 0.034 mg calcium/hour, respectively). These results indicated a ^{140}Ba preference for more trabecular bone. The authors concluded that ^{140}Ba is irreversibly deposited in bone since skeletal accretion of barium was about twice that of calcium, while the removal by reversible exchange reactions was approximately the same for barium and calcium.

Gutwein et al. (1974) examined barium retention in male Sprague-Dawley rats (275 g) exposed to combustion products from diesel fuel containing a barium-based antismoke additive and a tracer quantity of ^{133}Ba. The rats were exposed in a chamber with an average barium concentration of 1.39 mg/m^3 for a ten-hour period, resulting in an initial barium body burden of 0.1 μg/g (0.1 mg/kg) for tissue, minus the skin. The salt form of barium was not determined but was described as soluble in 0.1 N HCl. Whole-body retention decreased to approximately 45%, 35% and 25% of the initial retention at days 3, 8 and 24, respectively. While about 80% of the barium was cleared from the lungs by day 3, the level in bone increased through day 3 and remained elevated to more than 85% of total body burden (minus skin) throughout the 24-day study.

Cuddihy and Griffith (1972) determined the retention of $^{140}BaCl_2$ in beagle dogs after inhalation exposure (see Section III. A., Absorption, for experimental protocol details). Two days after exposure, whole-body retention was approximately 50% of the initial ^{140}Ba body burden; more than 95% of the retained ^{140}Ba was in lung, liver and skeletal tissues. Whole-body ^{140}Ba retention decreased to approximately 20%, 5% and 1% of initial body burden 16, 32 and 64 days after exposure, respectively, and was primarily (>90%) located in the skeleton. Cuddihy et al. (1974) repeated the above results up to 16 days after exposure (see Section III. A., Absorption, for details of the study). They also calculated the retention of $^{133}BaSO_4$ after inhalation exposure. Barium sulfate retention was 50% of initial body burden about seven days after exposure; approximately 10% of the initial body burden remained in the lungs and more than 30% was in the skeleton.

Early work by Rundo (1967) and Harrison et al. (1967) presented a three-component model to describe the retention kinetics of a tracer quantity of ^{133}Ba in a 60-year-old man after a single intravenous injection. Biological half-lives were calculated to be approximately 3.6 days (21.9% of injected dose), 34.2 days (4.1%) and 1,033 days (5.58%) for the three components. Experimental data showed the barium retention was 16.7%, 10.5% and 2.83% of the injected dose at 6, 15 and 1,000 days after administration.

Newton et al. (1977) continued to follow the retention of ^{133}Ba in the 60-year-old male over a ten-year period following administration. Analysis revealed an increasing divergence of observed and predicted retention of ^{133}Ba after day 1,000. Therefore, an additional, very-long-lived fourth component was fitted to the data to describe the long-term retention.

These data were also analyzed in terms of the model developed by the Task Group on Alkaline Earth Metabolism (ICRP 1973). Their multi-exponential analysis of the ^{133}Ba retention data yielded biological half-lives of 3.5 days (22.6% of the dose), 35.1 days (4.2% of the dose), 741 days (3.9% of the dose) and 8,000±4,900 days (1.6% of the dose) for the four components, representing primarily clearance from (1) body fluids and soft tissues, (2) bone surfaces, (3) trabecular bone, and (4) cortical bone, respectively. The cumulative fecal excretion was nine times the cumulative urinary excretion between days 8 and 28, and this ratio was used to calculate the systemic retention. The assumption of a ratio of four between the turnover rates of cancellous and compact bone for the ICRP model was supported by the authors' model. The authors noted that a ten-year period was too short for the half-life of the fourth component to be established accurately and that neither model gave a correct systemic retention for early time periods using whole-body counting methods.

Erre et al. (1980) developed a new model which used blood plasma data and predicted retention for the first few days after administration. Their seven-component model was identical to that of Newton et al. (1977) for periods greater than ten days.

Bauer et al. (1957) calculated skeletal accretion rates after ^{140}Ba and ^{45}Ca were injected intramuscularly into three children (two girls and one boy of ages 1 month, 1.5 years and 5 months, weighing 4.3 kg, 12.9 kg and 6.9 kg, respectively) and intravenously into an adult female (25 years old and 60 kg). Whole skeletal accretion rates calculated from ^{140}Ba and ^{45}Ca data were approximately 0.7 and 0.4 g calcium/day, respectively, for children and 0.57 and 0.47 g calcium/day, respectively, for the adult. The accretion rate in spongy bone (data obtained from the five-month-old boy) was about twice that of compact bone (0.0233 and 0.0126 g calcium per day/g calcium of bone sample, respectively).

The pigmented tissues from the eyes of cows, rabbits and men were examined by Sowden and Pirie (1958) for barium and strontium content. The results of the activation analysis of ashed tissue are shown in Table III-11. Barium was especially concentrated in the choroid, where the concentration increased most noticeably with age in the cow. The authors suggested that the presence of barium may be essential for vision and structure of the choroid.

Autopsy analysis of barium in human bone (Sowden and Stitch 1957) and nonskeletal tissues (Sowden 1958) was accomplished by neutron activation of the tissue in the ashed form. The results of analysis of 35 bone samples are shown in Table III-12. Barium content did not significantly increase with age. Average concentrations of barium in non-skeletal tissues are shown in Table III-13. Highest concentrations of barium were in the lung and aorta.

Dental enamel of the first bicuspids of humans less than 20 years of age was analyzed for 66 minor inorganic elements by spark source mass spectroscopy (Losee et al. 1974). Teeth were from 24 communities located in 16 states in the United States. Mean barium concentration was 4.2±0.60 μg/g (mg/kg) dry weight.

Table III-11 Barium Content of Eye Tissue[a]

Species	Cornea	Iris	Lens	Vitreous Body	Retina	Choroid	Tapetal Choroid	Sclera
Calf	39(0.39)	740(7.40) 617(6.17)	4(0.04)	33(0.33)	13(0.13) 5(0.05)	1730(17.3) 3080(30.8)	3728(37.28)	610(6.10)
Cow	70(0.70) 3(0.03)	18700(187.00) 20600(206.00)	5(0.05) 6(0.06)	-	56(0.56) 129(1.29)	20000(200) 66000(660)	17700(177.00)	1700(17.00)
Rabbit								
10 weeks	20(0.20)	196(1.96)	5(0.05)	1(0.01)	26(0.26)	303(3.03)	-	23(0.23)
6 to 9 mo	-	222(2.22) 590(5.90) 374(3.74)	-	-	11(0.11) 13(0.13) 20(0.20)	765(7.65) 775(7.75) 1050(10.50)	-	40(0.40) 28(0.28) 19(0.19)
Man								
Newborn	5(0.05)	25(0.25)	Detected	-	9(0.09)	9(0.09)	-	13(0.13)
49 to 86 yr	3(0.03)	-	5(0.05)	-	4(0.04)	24(0.24) 10(0.10)	-	30(0.30)

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[a] Results are expressed as μg/100 g wet weight, with mg/kg in parentheses. These are single estimations on combined tissues from several eyes.

Adapted from Sowden and Pirie (1958).

Table III-12 Concentration of Stable Barium in Bones of Human Males and Females

Age (number sampled)	Barium Concentration, ppm	
	mean ± S.D.[a]	range
0 to 3 months (7)	7.0±4.0	1.9-13.0
1 to 13 years (9)	7.6±7.0	2.1-21.0
19 to 33 years (9)	5.1±0.12	4.3-7.9
33 to 74 years (10)	8.5±4	3.7-17.3

[a] Standard deviation.

Adapted from Sowden and Stitch (1957).

Table III-13 Concentration of Barium in Human Tissues

Tissue	Mean Barium Concentration (μg/g of ash)[a]			
	Stillborn[b]	0-0.25 Year[b]	0.25-12 Years[b]	30-87 Years[b]
Liver	4.2 (7)		3.3 (3)	3.5 (15)
Brain	-		2.3 (6)	2.6 (12)
Spleen	-		3.5 (3)	3.3 (12)
Heart	3.1 (7)		20.3 (9)	7.4 (11)
Kidney	-	8.0 (5)	5.0 (3)	9.9 (14)
Lung	-	21.4 (7)	11.3 (9)	15.4 (10)
Pancreas	-		-	8.1 (6)
Testes	-		-	3.1 (7)
Ovary	-		-	1.7 (3)
Bladder	-	6.0 (4)	4.9 (8)	11.5 (10)
Muscle	-		6.3 (9)	7.1 (14)
Skin	-		10.3 (7)	13.3 (14)
Thyroid	-		1.2 (9)	23.8 (15)
Fat	-		-	8.5 (13)
Aorta	-		1000[c] (1)	28 (7)

[a] Also mg/kg of ash.
[b] Number of specimens in parentheses.
[c] One sample from a 10-year-old.

Adapted from Sowden (1958).

Schroeder et al. (1972) presented an analysis of barium content in human tissue at autopsy (from the analysis of Tipton and Cook, Health Phys. 9:103, 1963). The body contains approximately 22.0 mg of barium with 20.0 mg located in bone. Barium was present in every stillborn infant, and in every infant up to one year of age. Barium content was higher in the aorta, heart, kidney, liver, spleen and muscle in American infants (less than one year old) than in young American adults (1 to 19 years old). However, barium content in older American adults (more than 19 years old) gradually increased (except in the liver) to approximately the same concentration as in the infants. Barium concentrations in the lung were low at birth and increased with age (from approximately 5 ppm barium at birth to 25 ppm, in terms of ash, at 70 years of age). Brain and pancreas levels of barium were low at birth and did not change with time in American subjects. In comparison to American subjects, foreign subjects had higher barium concentrations in the aorta, brain, heart, kidney, pancreas and spleen (from the analyses of Tipton et al., Health Phys. 11:403, 1965). In addition, foreign subject barium content in these same tissues (except heart) decreased with increasing age, as opposed to the trend seen in the American subjects. Barium concentrations in various tissues from American males aged 20 to 59 years and from subjects of both sexes aged 20 years or more from other countries are shown in Table III-14. For almost all tissues examined, barium concentrations were higher in foreign subjects than in subjects from the United States.

There is no direct evidence indicating that barium is an essential element in humans. However, Schroeder et al. (1972) also determined the interrelationships of strontium and barium with other trace elements in human

Table III-14 Barium Concentrations in Human Tissues in Various Geographical Areas[a]

	Males 20 to 59 yr	Adults 20 yr or older			
	United States[b]	Africa	Near East	Far East	Switzerland
Aorta	7	15	19	11	15
Brain	<0.2	3.1	4.9	2.3	2.9
Heart	0.7	4.3	6.6	3.5	3.6
Kidney	1.2	4.9	12	5.0	4.0
Liver	<0.2	2.7	5.2	3.3	1.8
Lung	13	23	32	16	38
Pancreas	1.5	7.2	11	4.2	5.3
Spleen	0.5	4.5	9.1	3.2	4.4
Testis	1.0	20	12	5.0	21

[a] Median values as μg/g (mg/kg) in ash.
[b] From Schroeder et al. (1972).

Adapted from Tipton et al. (1965).

subjects. Paired rank correlations indicated that barium was significantly ($P<0.001$) associated with magnesium, chromium, manganese and copper. The authors noted that most essential trace elements are related to each other in human tissues and were surprised to find barium intimately related to essential elements in human soft tissues. These interrelationships raise speculation of some unknown essential requirement for barium. Further evidence would be necessary, however, to conclude that barium has an essential, beneficial effect in humans.

The barium content of the daily diets (including water and beverages) and total excreta of two men (23 years old, 100 kg, and 25 years old, 71 kg) over a 50-week period was examined by Tipton et al. (1969) by arc emission spectrography (Table III-7). Although the actual diets of the two individuals differed considerably, the patterns of excretion and balance at the end of 50 weeks were similar.

Earlier, Tipton et al. (1966) did a barium balance study over a 30-day period with female (34 years old, approximately 62 kg) and male (35 years old, approximately 75 kg) subjects (Table III-6). This study showed a larger difference in the barium balance between the two individuals than the longer study.

F. Summary

The rate of absorption of barium from the GI tract may be dependent on the species, the salt form, the contents of the GI tract, GI retention time, diet and the age of the exposed subject. Rats absorbed about 7% of intragastrically administered barium in seven hours while hamsters absorbed about 11% after four hours. The absorption of $BaCl_2$ by fasted rats was approximately 20%; this value was three times higher than that of fed rats. Administration of SO_4^{-2} to rats immediately following the barium dosage did not significantly change barium absorption. Additionally, less soluble barium salt forms were absorbed by fed rats after intragastric administration. Peak blood concentrations of $BaSO_4$ and $BaCO_3$ occurred 60 minutes after administration and were approximately 85% and 45%, respectively, of $BaCl_2$ concentrations. A milk sugar (lactose) and lysine significantly ($P<0.05$) increased barium absorption in 24-hour-fasted adult rats. Barium absorption was reduced to 12% to 25% of control by addition of sodium alginates to the diet. Very young rats fed a diet of maternal milk absorbed 85% of administered barium, while absorption was less than 10% in adult animals, demonstrating the possible susceptibility of the very young. The 1960 ICRP Committee II Report on Permissible Dose for Internal Radiation reported a GI absorption factor of barium in man of 5%.

Clearance of barium is dependent on its solubility (salt form or association with other materials) as well as the particle size and surface area. Barium chloride was readily absorbed through nasal tissue (approximately 60% of the dose after four hours) and lung tissue (about 50% after one hour), while $BaSO_4$ was cleared with a biological half-life of two to eight days. Barium in fused montmorillonite clay had the lowest clearance rate, over 400 days.

Barium is rapidly distributed via the plasma to the soft tissues, teeth and skeleton and across the placental barrier to the fetus. Soft tissue distribution was found to be generally in proportion to the tissue calcium content and tissue barium concentrations fell parallel to the concentration in blood. Exceptions were the salivary gland, cardiac muscle and melanin-containing tissues.

Deposition of barium in bone was found to occur more slowly than that in soft tissues, but retention was prolonged. Apparent transfer rates from blood to bone were two to four times higher for barium than for calcium. This preferential barium deposition occurred primarily in the active sites of bone growth and on bone surfaces. Total barium uptake into bone decreased in older animals.

Tissue bioaccumulation of barium occurred in animals after oral exposure and was found to increase with increasing barium concentration. However, the accumulation did not increase as the duration of exposure increased. Fractional whole-body retention of barium was approximately 35% of the dosage in rats 16 days after injection and 10.5% in man after 15 days. Multi-exponential analysis of the barium retention data in man yielded biological half-lives from 3.5 to 8,000 days. Retention of $BaCl_2$ after inhalation exposure decreased to about 1% of the dosage after 16 days, while the half-life of $BaSO_4$ in the lung is 8 to 9 days. Retention is primarily skeletal, and the skeletal accretion rate of barium is approximately two times that of calcium.

The body content of barium in reference man is 22 mg, of which 91% is localized in bone. Autopsy analysis of bone and non-skeletal tissues revealed no difference in barium content as a function of age. Human tissue barium concentrations vary with geographical location, with foreign subjects having higher barium levels than American subjects. Long-term balance studies in humans demonstrated a mean barium balance of zero (with a range of -0.80 to 0.89) in four subjects consuming 0.65 to 1.77 mg barium/day.

The skeletal metabolism of barium is qualitatively similar to and closely parallels that of calcium. Barium is excreted primarily in the feces. The ratio of total fecal excretion to total urinary excretion in humans is approximately 9:1. Barium is also excreted in the saliva (0.22% to 0.33%), in seminal fluid (0.81%) and in the milk of lactating cows.

IV. HUMAN EXPOSURE

Humans may be exposed to barium in drinking water, food and air. Detailed information concerning the occurrence of an exposure to barium in the environment is presented in another document entitled, "Occurrence of Barium in Drinking Water, Food and Air" (Letkiewicz et al. 1984). This Section summarizes the pertinent information presented in that document in order to assess the relative source contributions from drinking water, food and air.

A. Exposure Estimation

This analysis is limited to drinking water, food and air, since these media are considered to be general sources common to all individuals. Some individuals may be exposed to barium from sources other than the three considered here. Even in limiting the analysis to these three sources, it must be recognized that individual exposures will vary widely based on many personal choices and several factors over which there is little control. Where one lives, works and travels, what one eats and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Unfortunately, data and methods have not yet been developed to estimate exposure of identifiable population subgroups from all sources simultaneously.

To the extent possible, estimates are provided of the number of individuals exposed to each medium at various barium concentrations. The 70-kg man is used for estimating intake.

1. Drinking Water

Very limited data are available for characterizing human intake of barium from drinking water provided by public water supplies. Based on the information presented in Letkiewicz et al. (1984), it appears that, by far, most of the approximately 214 million people in the United States who use public water supplies are exposed to levels below 0.2 mg/L. While some individuals may be exposed to drinking water in which there is no barium, some information is available which suggests that many supplies do have barium present at levels ranging from 0.001 to 0.2 mg/L. There are too few data to reliably estimate the number of persons exposed to barium in drinking water at various levels below 1.0 mg/L, the current maximum contaminant level (MCL). However, based on the compliance monitoring data available through Federal Reporting Data System (FRDS), it can be estimated that approximately 150,000 people are receiving drinking water from public water supplies with levels above 1.0 mg/L.

2. Diet

The International Commission on Radiological Protection (ICRP 1974) reported dietary intake of barium to be 0.75 mg/day, including both food and fluids. The contribution from drinking water was estimated to be about 0.08 mg/day, which leaves 0.67 mg/day from non-drinking water dietary sources. In long-term studies, dietary intake (including beverages) of barium was found to be 0.9 mg/day, ranging from 0.44 to 1.8 mg/day. Absorption of barium from food is reported to be approximately 6% (ranging from 1% to 15%).

3. Air

The ICRP (1974) reported that intake of barium through inhalation ranges from 0.09 to 26 μg/day. Using the National Air Surveillance Network (NASN) mean data ranging from 0.0015 to 0.95 $\mu g/m^3$ (USEPA 1984) and an estimated ventilation rate of 23 m^3/day for the adult male, a respiratory intake range of 0.03 to 22 μg/day is calculated, which is comparable to the ICRP estimate. The NAS (1977) estimated that 75% of inhaled barium is absorbed into the bloodstream.

B. Summary

There is a very limited data base on human exposure to barium from drinking water, food and air. While some information is available that suggests the general range of barium intake from these three media, it is not possible to determine what proportion of the population have drinking water, dietary and respiratory intakes at various levels. For drinking water, it is possible to estimate the size of the population exposed to levels in public water supplies above 1.0 mg/L, the current MCL, but not for levels at or below 1.0 mg/L.

Consequently, a detailed relative source contribution assessment that describes the importance of each medium as a barium source for different segments of the U.S. population could not be developed.

While it is not possible to develop a detailed profile of human exposure and the relative source contributions from the three media of interest for barium, it is possible to show the relative importance of the three media for various assumed exposure conditions. Table IV-1 illustrates the relative source contributions for the adult male under several assumed conditions. The first set of conditions assumes what appear to be typical or moderate levels of exposure to barium from food and air based on the limited data available. These data suggest that when drinking water barium levels are below 0.2 mg/L, which appears to be the case for the majority of public water supplies, food is the predominant source. At 0.2 mg/L, drinking water would contribute approximately one-third of the daily dose. At the current MCL, however, drinking water would contribute over 70% of the daily dose of barium.

If the assumption is made that food and air intakes are at their highest reported levels, then food becomes an even more predominant source. Still, at 0.2 mg/L in drinking water, drinking water would be responsible for 16% of the daily dose, and at the current MCL, drinking water would contribute approximately 50% of the daily dose.

Table VI-1 Age-Specific Means and Standard Deviations of Systolic and Diastolic Blood Pressure Among White Persons 18 to 75+ Years of Age Living in West Dundee and McHenry, Illinois, 1976-1977

Blood Pressure	West Dundee						McHenry					
	Male			Female			Male			Female		
Age (yr)	No. Cases	Mean (mmHg)	SD[a]	No. Cases	Mean (mmHg)	SD[a]	No. Cases	Mean (mmHg)	SD[a]	No. Cases	Mean (mmHg)	Sd[a]
Systolic												
18-24	77	123.3	13.9	114	104.6	10.2	54	120.2	12.5	53	106.1	10.6
25-34	122	123.9	13.2	147	106.5	12.3	77	122.2	12.6	111	106.4	11.9
35-44	92	123.9	16.7	133	111.6	15.0	74	124.1	15.2	88	111.3	17.0
45-54	89	127.9	16.2	91	121.3	17.5	75	129.7	15.3	90	116.3	18.6
55-64	69	131.3	21.4	75	128.1	21.1	77	135.6	17.8	136	129.5	22.3
65-74	29	139.1	20.1	60	138.1	21.0	128	140.7	21.0	137	136.2	20.4
75+	28	149.8	20.3	49	151.6	23.4	47	144.8	22.0	56	146.1	21.3
Total Pop.[b]	506	129.7	17.8	669	120.7	21.5	532	129.8	19.2	671	119.6	22.8
Diastolic												
18-24	77	73.9	10.7	114	70.1	7.9	54	71.5	10.9	53	72.9	6.7
25-34	122	76.8	10.7	147	73.4	9.9	77	78.4	10.4	111	74.6	11.0
35-44	92	82.7	10.4	133	77.3	11.5	74	82.6	11.1	88	79.6	11.6
45-54	89	84.0	11.3	91	83.5	11.1	75	85.8	11.4	90	81.5	14.1
55-64	69	82.7	13.1	75	84.4	14.9	77	86.1	12.7	136	87.0	15.1
65-74	29	82.1	13.8	60	85.8	14.5	128	85.8	13.4	137	86.6	14.7
75+	28	80.4	10.1	49	88.0	14.6	47	81.7	12.5	56	83.4	16.5
Total Pop.[b]	506	80.4	11.8	669	79.7	13.1	532	81.8	12.7	671	80.6	14.4

[a] SD = standard deviation.
[b] Total sex-specific means are age-adjusted to the total sample size for each sex.

Adapted from Brenniman et al. (1981).

V. HEALTH EFFECTS IN ANIMALS

This section discusses the acute and chronic effects of barium exposure and is divided into six parts: acute toxicity, chronic toxicity, teratogenicity, mutagenicity, carcinogenicity and reproductive/embryotoxic effects. The acute toxicity section will be subdivided even further to include the effects of barium on various systems. The chronic toxicity section will also include those studies dealing with subchronic barium exposure, in addition to the chronic studies.

A. Acute Toxicity

The acute toxicity of barium to animals has been well documented. Since the objective of this report is to determine the dose range producing minimal health effects, the studies defining lethal doses will not be discussed in detail and are summarized in Table V-1.

The lethal doses for various barium compounds are dependent on the compound, route of administration and species (Table V-1). Variation in absorption after oral administration of acetate, chloride or nitrate barium salts probably reflects gastrointestinal uptake efficiencies, diet and physiologic responses. Rats given $BaSO_4$ intragastrically died, only after the dosage reached 25% to 50% of body weight, from stomach rupture (Boyd and Abel 1966). Details of this study were previously presented in Section IV.A., Absorption. Death occurred after the appearance of convulsions or cyanosis and subsequent respiratory failure. During the first 24 hours after barium

Table V-1 Acute Toxicity of Barium Salts

Compound	Species	Route	Dose	Barium Dosage (mg/kg)	Ref.
Barium Acetate	Mice (Swiss-Webster)	IV	LD_{50}	11.32±0.18	a
	Mice (ICR)	IV	LD_{50}	23.31±0.40	a
	Rabbit	OR	LD(1 day)	236	b
		OR	LD(1 day)	127	c
		OR	LD(1 hr)	438	c
		SC	LD	51.6	c
		IV	LD	6.4	c
Barium Chloride	Mice (Swiss-Webster)	IV	LD_{50}	8.12±1.51	a
	Mice (ICR)	IV	LD_{50}	19.20±1.02	a
	Mice	OR	LD	69.2	c
		IVT	LD_{50}	2.32-3.27	d
	Rat	SC	LD	44.2	c
		SC	LD	31.3-62.6	c
	Rat (weanling)	OR	LD_{50}	220	e
	(adult)	OR	LD_{50}	132	e
	Rabbit	OR	LD	170	b
		SC	LD	38	c
		IV	LD	9.9	c
	Cat	SC	LD	33	c
	Dog	OR	LD	59.4	b
		SC	LD	10	c
	Guinea Pig	SC	LD	36.3	c
	Horse	OR	LD	800-1200	b
Barium Carbonate	Rat	OR	LD	50-200	b
	Rabbit	OR	LD	170-300	b
	Mice	OR	LD	200	b
Barium Hydroxide	Chicken	IV	LD_{50}	623±156	f
Barium Nitrate	Mice (Swiss-Webster)	IV	LD_{50}	8.49±0.14	a
	Mice (ICR)	IV	LD_{50}	20.10±0.34	a
Barium Silicofluoride	Rat	OR	LD_{50}	175	b
	Rabbit	OR	MLD	175	b

LD = Lethal dose
Route: IV = Intravenous
IVT = Intracerebroventricular
OR = Oral
SC = Subcutaneous

LD_{50} = Lethal dose to 50% of test group
MLD = Minimum lethal dose which kills 1 of test group

[a] Syed and Hosain 1972
[b] Miner 1969
[c] Venugopal and Luckey 1978
[d] Segreti et al. 1979
[e] Tardiff et al. 1980
[f] Johnson et al. 1960

administration survivors exhibited clinical signs of toxicity which increased with the $BaSO_4$ dosage. Toxicity signs disappeared by 72 hours after administration. Studies using intravenous administration indicate that there is wide variability in the lethal dose of barium among species, as well as between strains of the same species. White mice exhibited an LD_{50} of the acetate, chloride and nitrate salts of barium that was two times that of the Swiss-Webster strain. Additionally, an age-specific effect of acute barium toxicity in rats was reported by Tardiff et al. (1980). The LD_{50} was 500 mg/kg $BaCl_2$ (220 mg barium/kg) for weanling rats and 300 mg/kg $BaCl_2$ (132 mg barium/kg) for adult rats after administration as a single dose by gavage (animals were observed for 14 days after dosing). It is interesting to note that a larger barium dosage was necessary to cause death in the weanlings than the adult animals, since the young are generally more susceptible to metal toxicities than adults.

1. Cardiovascular System

Introduction of 0.1 to 1.0 millimol $BaCl_2$/kg (calculated to be 20.7 to 207 mg/kg) by gastric tube or 0.03-0.1 millimol $BaCl_2$/kg (calculated to be 6.2 to 20.7 mg/kg) intravenously into fasted (time not specified) dogs (weight, age and sex not specified), produced signs of barium toxicity (Chou and Chin 1943). The authors noted that when barium was administered by mouth the more severe symptoms were those of the GI tract, and cardiac and respiratory symptoms were rare. However, cardiac symptoms such as ventricular extrasystoles, arrhythmia, elevated blood pressure and tachycardia were distinctive features after barium infusion, while GI symptoms were less striking. The cardiovascular symptoms disappeared about 30 minutes after cessation of barium injection. The authors noted that if excessive amounts of barium were administered rapidly, atrioventricular block and fibrillation resulted in immediate death.

Intravenous infusion of $BaCl_2$ at a rate of 1.0 µmol/kg/min (calculated to be 0.207 mg/kg/min) into anesthetized mongrel dogs (6 to 22 kg, both sexes) produced hypokalemia, elevated blood pressure and electrocardiographic changes (Roza and Berman 1971). The following were the signs of barium toxicity elicited in rough chronologic order: (1) arterial hypertension and premature supraventricular and ventricular contractions appeared within five minutes (at five minutes the total dose of $BaCl_2$ was calculated to be 1.035 mg/kg), (2) skeletal muscle contractions and GI symptoms (salivation and diarrhea), and (3) more severe ECG changes with multiple premature ventricular contractions and flaccid paralysis of respiratory muscles. If respiration was assisted, the final cardiac events were ventricular tachycardia and fibrillation followed by death. The blood pressure increased from an average of 138/86 to 204/130 mm Hg. Potassium infusion reversed the toxic effects of barium. However, the initial symptom of barium infusion, hypertension, was unaffected by potassium infusion, bilateral nephrectomy or simultaneous administration of phentolamine. The authors suggested that these results indicated a direct arteriolar stimulation by barium in addition to its hypokalemia-inducing effect.

Foster et al. (1977) noted that accelerated ventricular escapes (AVE) were produced in 18 of 23 dogs by a mean concentration of 20.2 µmol/kg (calculated to be 4.18 mg/kg) $BaCl_2$ (doses ranged from 3.6 to 64.7 μmol/kg) infused intravenously at a rate of 3 to 4 μmol/kg/min (calculated to be 0.62 to 0.83 mg/kg/min) into adult mongrel dogs (either sex, weight not specified). Continuation of infusion resulted in ventricular tachycardia. The mean dose of $BaCl_2$ infused in five animals that did not develop AVE was 39 μmol/kg (calculated to be 8.07 mg/kg). Mean serum potassium decreased with barium infusion, and potassium infusion terminated the tachycardia. Direct injection of less than 2 mL of a 10^{-2} M solution of $BaCl_2$ (0.414 mg/kg, assuming an average 10-kg weight) into the left anterior descending coronary artery avoided the systemic hypertension effect described by Roza and Berman (1971).

Intravenous infusion of $BaCl_2$ (less than 16 to 25 mg/kg at a rate of 0.5 mg/min) into anesthetized Wistar rats of either sex (150 to 250 g) elicited stimulation of the musculature (Schott and McArdle 1974). The characteristic manifestations described by Roza and Berman (1971), including rapid and significant hypokalemia and hypertension (the blood pressure sometimes doubled within three minutes), were also noted in this study. Hypertension occurred at all barium dosages, regardless of the presence or degree of paralysis, and was not affected by the administration of propranolol, $CaCl_2$, potassium chloride (KCl), or ouabain or by bilateral adrenalectomy. The importance of dosage and infusion rate were demonstrated in this study. Since the fatal acute dose was close to the effective acute dose, the lethality of the dosage depended on the course of administration.

2. Striated Muscles

Chou and Chin (1943) noted that dogs receiving orally administered $BaCl_2$ exhibited neuromuscular symptoms of twitching, tremor and motor weakness followed by paralysis in severe poisoning (details of this study were presented in Section V. A. 1., Cardiovascular System). Dogs receiving $BaCl_2$ by intravenous administration produced motor symptoms more gradually (after one to two hours) and, in contrast to oral administration, motor weakness was more apparent than paralysis.

Anesthetized Wistar rats (either sex, weighing 150 to 250 g) were given intravenous infusions of $BaCl_2$ (Schott and McArdle 1974) and contractions of the gastrocnemius/plantaris/soleus muscle group were measured. Contractions were elicited either directly or indirectly by electrical stimulation of the distal end of the cut sciatic nerve. The effective paralyzing dose of $BaCl_2$ was 16 to 25 mg/kg, administered at a rate of 0.5 mg/min. Lower doses of barium produced only initial muscle stimulation. The barium plasma concentration during the course of the experiment was 5 to 100 μg $BaCl_2$/mL. The time course of paralysis development correlated well with hypokalemia production, but not with the plasma barium concentration. The development of paralysis was unaffected by the administration of propranolol, $CaCl_2$, or ouabain (5 to 10 μg/kg) or by bilateral nephrectomy.

Intravenous infusion of $BaCl_2$ at approximately 1.0 μmol/kg/min (calculated to be 0.207 mg/kg/min) into anesthesized dogs produced generalized muscle twitching followed by flaccid paralysis (Roza and Berman 1971). Higher infusion rates produced paralysis within a few minutes and death from respiratory paralysis. Details of this study are presented in Section V. A. 1., Cardiovascular System.

3. Nervous System

The effect of barium on the central nervous system (CNS) was studied by examining the electroshock thresholds for convulsions prior to and following barium administration (Peyton and Borowitz 1978). Male albino Swiss-Webster mice (20 to 25 g) exhibited increased convulsive electroshock sensitivity when tested 0.5 hour after intraperitoneal barium administration (6.6 and 20 mg/kg) and decreased sensitivity when tested after 24 hours (2, 6.6 and 20 mg/kg).

The effects of barium on distribution of ^{45}Ca and barium in subcellular fractions of whole mouse brain were also determined by Peyton and Borowitz (1979). The ^{45}Ca in the synaptosomal and myelin fractions was increased ($P<0.05$) at 0.5 hour after intraperitoneal barium administration (20 mg/kg), but synaptosomal content decreased ($P<0.05$) at 24 hours when compared to control. Other subcellular fractions showed no significant changes ($P>0.05$). At 0.5 hour after intraperitoneal barium administration (20 mg/kg containing ^{131}Ba), the distribution of barium across brain fractions was relatively constant. The barium concentration was significantly ($P<0.05$) greater 24 hours after administration, especially in the mitochondrial fraction ($P<0.01$). The high mitochondrial barium concentration did not affect the concentration of ^{45}Ca in this study. The uniform distribution at 0.5 hour may reflect the ease with which barium crosses biological membranes. The authors suggested that at

0.5 hour after administration barium appeared to cause a potassium-like depolarization in the CNS. This may explain the increased electroshock sensitivity at 0.5 hour. The decreased sensitivity at 24 hours was suggested to be due to barium accumulation in the brain, where it may mimic calcium's ability to depress neuronal excitability.

Intracerebroventricular administration of $BaCl_2$ was found to produce severe convulsions that progressed to a final tonic-extensor convulsion and then death in lightly anesthetized male Swiss-Webster mice (25-35 g) (Segreti et al. 1979). The LD_{50} ($P<0.05$) of $BaCl_2$ at 10 minutes post-administration was 0.597 µmol/mouse (calculated to be 3.5 to 4.9 mg/kg). Antagonism of $BaCl_2$-induced convulsions and lethality was obtained by pretreatment with atropine (1 to 5 mg/kg administered intraperitoneally) or naloxone (1 to 5 mg/kg administered subcutaneously) 10 minutes before barium administration.

4. Secretory Processes

The influence of barium ($BaCl_2$) on calcitonin release from the thyroid was examined after intravenous infusion into a young male Yorkshire pig (10 kg) and after incubation with porcine thyroid slices or perfusion of isolated whole porcine thyroids (Pento 1979). As determined by radioimmunoassay, plasma calcitonin was increased 2.5 times and 5 times, respectively, during two separate 20-minute perfusions of 1.7 mg/kg/min of $BaCl_2$ (34 mg/kg) performed on separate days. The perfusion was discontinued due to severe cardiotoxicity.

In vitro studies by Pento (1979) showed that 2.5 and 5 mM $BaCl_2$ significantly ($P<0.005$) increased calcitonin secretion over control values in porcine slices, although there was no significant difference between the levels produced by the two different barium doses. Calcium chloride (2.5 mM) produced approximately twice the secretory response of equimolar $BaCl_2$. Whole thyroid perfusion with 5 and 10 mM $BaCl_2$ seemed to increase calcitonin release in a dose-dependent manner. Since only two concentrations were examined, a dose-dependent relationship was difficult to verify.

Acutely denervated cat adrenal glands were perfused in vivo with 2 or 5 mM $BaCl_2$ to investigate the effects of barium on release of catecholamines from the glands (Douglas and Rubin 1964a,b). Barium evoked an intense secretory response, commonly more than 100 times control levels. The stimulant action of barium persisted in the presence of the chelator ethylenediaminetetraacetic acid (EDTA). Stimulant action also persisted in the presence of hexamethonium in sufficient concentration to block indirect stimulatory actions of the splanchnic nerves. Removal of calcium from the perfusate eliminated the stimulant action of acetylcholine and excess potassium, but not of barium. Furthermore, barium stimulated secretion of catecholamines in the presence of 2 mM calcium. Addition of excess calcium to a 2 mM calcium perfusate did not produce any further stimulation. Therefore, the authors concluded that barium has some additional action not shared by calcium. They suggested that barium produces an alteration in the membrane by displacing bound calcium. This increases membrane permeability to barium, explaining the release of catecholamines in the absence of an external stimulus (excess potassium ions or acetylcholine).

The influence of barium on neurotransmitter release from the splenic nerve of the cat (age, weight and sex not specified) in situ was examined by Kirpekar and Misu (1967). The splenic nerve was electrically stimulated, and released noradrenaline was assayed fluorometrically and biologically. Electrically evoked noradrenaline release was calcium-dependent. However, substitution of 2.5 mM barium for 2.5 mM calcium nearly doubled noradrenaline output and also increased the basal secretion rate at rest. The authors suggested that the barium effect on release of transmitter may have been partly due to the membrane depolarizing action of barium.

Boullin (1965, 1967) examined the effect of divalent cations on the release in situ of ^{3}H-labeled noradrenaline by sympathetic nerves in the colon of cats (2 to 4 kg, sex not specified). Post-ganglionic inferior mesenteric nerve stimulation in the presence of calcium (1.5 to 10.0 mM) produced an efflux of ^{3}H-labeled noradrenaline from the nerve endings into the perfusion medium. The response was abolished during perfusion with solutions containing no calcium ions (Ca^{+2}). Replacement of Ca^{+2} (2.5 mM) with barium (5 mM) evoked a spontaneous release of ^{3}H-labeled noradrenaline and an increase in efflux of noradrenaline upon nerve stimulation. The author suggested that barium may tightly bind to the tissue since nerve stimulation caused noradrenaline release during perfusion in Ca^{2+}-free solution up to 30 minutes after barium removal.

5. Antagonistic Action

The barium ion appears to be a physiologic antagonist of potassium.

Symptoms of barium toxicity follow the production of a barium-induced hypokalemia. Roza and Berman (1971) infused $BaCl_2$ into 13 mongrel dogs, noted the signs of toxicity and measured serum and urinary potassium levels (see Section V. A. 1, Cardiovascular System, for study details and signs of toxicity). Total dosages of 22 to 154 µg/kg (0.022 to 0.154 mg/kg) were infused over periods of 20 to 100 minutes. Cessation of infusion was determined by an abnormal ECG. Each dog responded with decreases in serum potassium ranging from 2.1 to 0.3 mEq/L, but neither urine flow nor urinary potassium excretion changed significantly.

In another experiment by Roza and Berman (1971), serum and red cell potassium levels were measured after infusion of saline solution and/or $BaCl_2$. The calculated total dosage of $BaCl_2$ was 15.9 to 135 µmol/kg (3.29 to 27.95 mg/kg), administered at 0.36 to 2.0 µmol/kg for 30 to 100 minutes. The serum potassium in those dogs decreased significantly ($P<0.005$) from 2.87±0.16 to 1.89±0.14 mEq/L while red blood cell potassium increased significantly ($P<0.01$) from 5.64±0.32 to 6.46±0.39 mEq/L. The production of hypokalemia was unaffected by bilateral nephrectomy. These data indicate that hypokalemia (1) was barium induced, (2) was a result of extracellular potassium transfer into the intracellular compartment (rather than urinary K^+ loss), and (3) occurred prior to cardiovascular changes. All signs of barium toxicity except hypertension were abolished by KCl infusion, suggesting a physiologic antagonism between barium and potassium.

Foster et al. (1977) also infused $BaCl_2$ (mean 20.2 µmol/kg, calculated to be 4.18 mg/kg) into dogs and noted a decrease in serum potassium from 3.4

mEq/L to 2.8 mEq/L at the onset of ECG changes. Continued infusion of $BaCl_2$ produced tachycardia which was terminated by KCl infusion. This study was discussed in more detail in Section V. A. 1., Cardiovascular System.

Wistar rats developed hypokalemia with barium infusion that the authors described as "striking" in both degree and rapidity of onset (Schott and McArdle 1974). Details of this study have previously been presented in Sections V. A. 1., Cardiovascular System, and V. A. 2., Striated Muscles. The symptoms of barium toxicity, especially effects on striated muscle, were noted. Initial muscle stimulation was followed by a progressive decrease in muscle responsiveness, developing into flaccid paralysis. Five treated animals that recovered from barium-induced paralysis had serum potassium concentrations that decreased from 3.9 mEq/L to 1.8 to 2.3 mEq/L. The time course of development of paralysis correlated well with that of hypokalemia, but not with barium plasma concentrations. Injection of KCl into the artery of the muscle group increased muscle contraction.

B. Chronic Toxicity

This section is divided into subchronic and chronic studies. In this document, subchronic studies entail barium exposures for one year or less while chronic studies entail exposure for more than one year.

1. Subchronic Studies

A study of the subchronic toxicity of $BaCl_2$ administered in drinking water was performed with four-week-old Charles-River rats of either sex

(Tardiff et al. 1980). Males weighed from 115 to 136 g and females weighed from 95 to 111 g. Animals were exposed to 0, 10, 50 and 250 ppm barium (mg/L) in drinking water for 4, 8 or 13 weeks. The highest dose was one third of the determined LD_{50}. The calculated cumulative doses of barium after 13 weeks are shown in Table III-9, and the estimated doses after 4 and 8 weeks are shown in Table III-10. The background daily dose of barium from feed was approximately 0.5 μg/kg (0.0005 mg/kg).

Food consumption, clinical signs of toxicity (e.g., appearance of flaccid paralysis), body weight, hematologic parameters, serum enzyme activities, serum ions (K^+, Na^+ and Ca^{+2}), gross pathology and histopathology did not differ significantly from control groups. The authors noted that absolute and relative weights of lungs, livers, kidneys, spleens, hearts, femurs and brains of animals exposed to barium for 8 and 13 weeks were not significantly different from those of control animals. The relative weights of the adrenals were significantly ($P<0.05$) less than controls in males treated for 8 weeks at 50 and 250 ppm barium and females treated for 8 and 13 weeks at 250 ppm barium. The effect did not appear to be dose-related. The authors noted that the water consumption of animals in the high-dose group (250 ppm barium) was less than that of the corresponding controls and low-dose animals (10 and 50 ppm barium). In comparison to the high-dose group (250 ppm barium), male controls consumed 43 and 11 mL/kg/day more water and female controls consumed 63 and 11 mL/kg/day more water at the beginning and end of the study, respectively. Barium body burden increased substantially with increased exposure levels, but the final barium concentrations did not significantly differ with duration of exposure (see Table III-8).

Perry et al. (1983) studied the effect of barium in drinking water on blood pressure in 195 female weanling Long-Evans rats. These animals were maintained in large stainless steel cages in a low contamination environment and fed a rye-based diet with low trace metal content. Their drinking water contained five essential minerals (1 ppm Mo, 1 ppm Co, 5 ppm Cu, 10 ppm Mn, 50 ppm Zn) and $BaCl_2$ (0, 1, 10 or 100 ppm). No obvious signs of barium toxicity (e.g., flaccid paralysis) were noted. Control animals grew from a mean weight of 0.170 kg at one month to 0.435 kg at 16 months. The authors state that animals receiving barium did not show any change in food or water intake or in weight gain but no data were supplied. Blood pressure was measured in unanesthetized animals by the tail cuff procedure. The results are shown in Table V-2. No change in mean systolic blood pressure was seen in rats receiving 1 ppm $BaCl_2$ (average dose = 0.071 to 0.051 mg/kg/day) for up to 16 months. Rats receiving 10 ppm (average dose = 0.71 to 0.51 mg/kg/day) developed significant ($P<0.01$) increases in mean systolic blood pressure of 6, 7 and 4 mm Hg after 8, 12 and 16 months, respectively (0.60, 0.57 and 0.51 mg Ba/kg/day). Rats receiving 100 ppm (average dose = 7.1 to 5.1 mg/kg/day) displayed significant ($P<0.001$) increases in mean systolic pressure after only one month of treatment and at all subsequent measurements. A portion (12 to 13 rats) of each barium dosage group and 21 control rats were sacrificed at 1, 4 and 16 months, and the barium content of heart was measured. At four months, cardiac tissue from control rats contained 0.10 pg barium/g wet weight, while tissue from rats receiving $BaCl_2$ (1, 10 and 100 ppm) contained 0.14 (not significant), 0.14 (not significant) and 0.58 ($P<0.001$), respectively. The

Table V-2 Effects of Barium in Drinking Water on Mean Systolic Blood Pressure in Rats

Exposure (months)	Ba^{2+} in H_2O (ppm)	Av. Dose[a] mg/kg bw	Change[b] in Mean Systolic Pressure (mm Hg)	P
1	1	0.071	1	N.S.
	10	0.71	3	N.S.
	100	7.1	12	<.001
2	1	0.066	-1	N.S.
	10	0.66	1	N.S.
	100	6.6	6	<.001
4	1	0.063	1	N.S.
	10	0.63	5	N.S.
	100	6.3	12	<.001
8	1	0.060	2	N.S.
	10	0.60	6	<.01
	100	6.6	15	<.001
12	1	0.057	1	N.S.
	10	0.57	7	<.01
	100	5.7	16	<.001
16	1	0.051	1	N.S.
	10	0.51	4	<.01
	100	5.1	16	<.001

[a] Daily dose calculated from the mean weight and daily water intake of control rats.

[b] Compared to rats of the same age receiving no barium in the water.

Adapted from Perry et al. (1983)

authors indicate similar results were obtained at 1 month and 16 months, but no data were given.

Rats exposed to 100 ppm barium for 16 months had depressed rates of cardiac contraction and depressed electrical excitability. For these rats, the barium-induced increase in mean systolic blood pressure was evident under ketamine and xylazine anesthesia but absent with pentobarbital (45 mg/kg). In the rats exposed to 100 ppm barium for 16 months, cardiac ATP, phosphocreatine and phosphorylation potential were decreased, and ADP was suggestively increased (as measured by ^{31}P-NMR spectroscopy). No measurements of contractility, conduction or phosphatic metabolites were sought for the rats exposed to 1 or 10 ppm barium.

This study demonstrates a dose-response relationship between low-level barium exposure in drinking water and hypertension in female rats. Rats drinking water containing 10 mg/L (approximately 0.51 mg Ba/kg/day) developed a slight increase in mean systolic blood pressue (4 mm Hg) in 16 months. Rats receiving water with 100 mg/L of barium developed hypertension after one month and blood pressure increased throughout the 16 month study period. Cardiotoxic effects at 100 mg/L were also noted. A limitation of this study is the minimized exposure to other metals in the food, water and laboratory environment. Because of the interactions of barium with other trace metals, the restricted exposure to other metals may have contributed to the toxicity of barium.

Johnson et al. (1960) found that one-week-old chickens (male and female) could tolerate barium concentrations (hydroxide or acetate salt) up to 1,000 ppm in their diets for three weeks without apparent ill effects. Assuming that 1 ppm barium in food equals 0.125 mg barium/day for 21 days, the estimated total barium dosage was 2,625 mg/kg. A slight depression of growth was seen at 2,000 ppm (5,250 mg/kg total) and 4,000 ppm (10,500 mg/kg total), but no increase in mortality was apparent. More than half of the chickens receiving 8,000 ppm (21,000 mg/kg total) barium during the feeding period died. All chickens receiving 16,000 ppm and 32,000 ppm barium died after an average of seven days (14,000 mg/kg total) and five days (20,000 mg/kg total), respectively.

The effects of inhalation intoxication of albino rats (sex, strain and weight unspecified) with $BaCO_3$ dust in the chamber for one month (continuous exposure at a concentration of 33.4±3.6 mg/m^3) or for four months, (exposure six times a week for four hours a day at a concentration of 5.2±0.25 mg/m^3) were examined by Tarasenko et al. (1977). The authors state that animals exposed to barium for one month showed changes in their red and white blood cell picture, influence on metabolism and vascular tonus, and a reduction in the detoxifying function of the liver. Pathomorphological examinations of the organs revealed desquamative bronchitis and focal thickenings of the interalveolar septa in the lungs.

The results of the four-month exposure are shown in Table V-3. The data indicate the experimental group had increased arterial blood pressure,

Table V-3 Effects of Barium Inhalation on Rats after Exposure Six Times a Week for Four Hours a Day

	Weight (g)	Arterial Blood Pressure (mm Hg)	Hemoglobin (%)	Leukocytes ($x10^3/mm^3$)	Thrombocytes ($x10^3/mm^3$)	Calcium In Urine (% mg)
Control	292.0±8.5	92±2.0	84.4±0.8	13.5±0.7	259.5±3.2	3.3±0.15
Experimental	231.0±7.4	121±3.0	75.0±0.9	18.9±0.8	244.3±2.1	5.7±0.12

Blood Serum Parameters

	Sugar (mg %)	Phosphorus (mg %)	Total Protein (g %)	Cholinesterase (U of ext $x10^2$)	Alkaline Phosphatase (mg inorg. P)
Control	180.0±7.7	120.4±3.5	9.0±0.2	32.6±0.5	17.0±3.0
Experimental	110.0±7.0	130.0±2.5	7.2±0.1	22.1±0.6	26.3±1.0

[a] Results are expressed as the mean ± standard deviation.

Adapted from Tarasenko et al. (1977).

leukocyte count, blood phosphorus level and urinary calcium level. Total hemoglobin and protein in the blood decreased. Experimental animals also weighed less than controls at the end of the exposure period. The number of animals utilized in the study was not indicated.

2. Chronic Studies

Schroeder and Mitchener (1975a,b) examined the effects of chronic low-level barium exposure in drinking water. Random-bred Long-Evans rats (75 to 80 days old) and Charles River CD strain Swiss mice (19 to 20 days old) were given 5 mg Ba/L as barium acetate in drinking water for the lifetime of the animals (estimated lifetime totals of 164 and 587 mg Ba/kg, respectively). (Total barium dosage was calculated by assuming that rats and mice live approximately 24 months and that 5 mg/L equals 0.250 and 0.825 mg Ba/kg/day, respectively.) The rats (52 of each sex) showed no significant difference in median life-span, tumor incidence or serum uric acid. Proteinuria occurred in experimental male rats to a greater extent than in male controls ($P<0.05$, by Chi-square analysis) at 173 days of age. Experimental female rats exhibited increased growth at four intervals (120, 150, 180 and 540 days old) when compared to controls ($P<0.001$, by Student's t test). Significant decreases in fasting serum glucose levels occurred in exposed male rats at 532 ($P<0.005$) and 773 ($P<0.01$) days of age and in females at 98 ($P<0.05$) days of age. Fasting serum cholesterol values of exposed female rats were significantly higher ($P<0.001$) than controls at 532 and 773 days of age. Male mice (group of 54) showed a slight reduction in longevity (defined as the mean age of death of the last surviving 10% of the animals, or in this case 5 animals). There was no difference in tumor incidence, edema or blanching of incisor teeth in male or female mice (54 animals of each sex) exposed to barium when compared to controls.

C. Teratogenicity

Ridgway and Karnofsky (1952) studied the effects of metals on White Leghorn chick embryos (sex and number of embryos used were not indicated). The introduction of a single 20-mg dose of $BaCl_2$ (in a volume of 0.05 to 0.2 mL) into the yolk sac or into the chorioallantoic membrane at eight days produced an inhibition in the growth of the toes. This abnormality was present in approximately 50% of the barium-treated embryos surviving to 18 days, when they were sacrificed and examined. No other abnormalities were apparent on gross examination. Embryos injected on day four showed no abnormalities. No other information was presented in the report.

D. Mutagenicity

Studies of the mutagenicity of barium in animals have not been published. However, Sirover and Loeb (1976a,b) tested the ability of $BaCl_2$ (2, 6, 10 mM) and barium acetate (10 mM) to affect the accuracy of DNA synthesis *in vitro*. In a system containing synthetic polynucleotide templates and purified avian myeloblastosis viral DNA polymerases, barium did not affect DNA replication. The authors classified barium as non-mutagenic. Nishioka (1975) utilized a bacterial test to screen a number of metal compounds for possible mutagenesis. Barium at 5 mM had no effect on the system. It should be noted that large amounts of phosphate and sulfate salts were added to the nutrient media. These salts could have interacted with barium to decrease the soluble barium concentration.

E. Carcinogenicity

Life-term studies evaluated the health effects of trace elements in drinking water in rats and mice (Schroeder and Mitchener 1975a,b). The experimental details of this study were discussed in Section V. B. 2., Chronic Studies. They noted that Swiss Charles River CD mice (19 to 20 days old) or random-bred Long-Evans rats (75 to 80 days old) exposed to 5 mg/L barium acetate in drinking water for a lifetime (totals of 587 and 164 mg barium/kg, respectively) did not increase the incidence of tumor production. This conclusion was derived from measurements of tumor production on gross examination of autopsied animals.

F. Reproductive/Embryotoxic Effects

The introduction of a single 20-mg dose of $BaCl_2$ into eight-day-old White Leghorn chick embryos produced an inhibition of toe growth in 50% of the embryos surviving to 18 days of age (Ridgway and Karnofsky 1952). No other abnormalities were seen.

Male rats (species, age and weight unspecified) inhaling $BaCO_3$ at a concentration of 22.6±0.6 mg/m^3 during one cycle of spermatogenesis or at a concentration of 5.2±0.25 mg/m^3 for four months experienced some disturbances of spermatogenesis (Tarasenko et al. 1977). No other details of the study were provided. The actual numbers were not given, but the authors stated that a decrease was observed in the total number of spermatozoids, the percentage of motile forms and the duration of their mobility. In addition, they stated that a three-fold increase in embryonal mortality was observed in females mated with males exposed to $BaCO_3$ inhalation for four months.

Tarasenko et al. (1977) also examined the effects of $BaCO_3$ inhalation (13.4±0.7 mg/m^3 or 3.1±0.16 mg/m^3) for four months on female rats (age and weight unspecified), and the effects of 1/16 the LD_{50} of 418 mg/kg $BaCO_3$ (a dosage of 26.13 mg/kg) given orally 24 days before conception and during the entire pregnancy (dosage interval not indicated). No other details of the study were provided. The authors stated that the non-pregnant rats exposed to 13.4±0.7 mg/m^3 showed a mean decrease in the estrus cycle duration before experiment termination. These rats had underdeveloped offspring (at an undesignated time after inhalation barium exposure) that showed increased mortality and decreased weight gain during the first two months of life when compared to controls. Pregnant female rats receiving $BaCO_3$ orally delivered offspring that had increased mortality for a period of two months after birth. Examination of the young revealed an increased blood leukocyte count and a disturbance in the synthetic function of the liver (using the Quick-Pytel test). All of those findings indicate that barium has an embryotoxic effect.

However, Tarasenko and co-workers failed to include enough data and details to allow readers to draw their own conclusions about the effects of barium.

G. Summary

Wide variability exists in the acute toxicity of barium, depending on the dosage form, route of administration, species, strain of the species and age. Barium exhibits a steep toxicity curve. Generally the toxicity of the barium salt tends to increase as a function of the solubility of the barium salt in biological fluids. Acute animal barium poisonings have demonstrated that the clinical signs of barium toxicity are due to profound stimulation of cardiac, striated and smooth muscle. Hypokalemia, elevated blood pressure and ECG changes (showing increasing frequency of ectopic beats) appear initially, followed by neuromuscular and GI symptoms. Neuromuscular weakness and ECG changes become more severe as the dosage of barium increases, until respiratory paralysis, ventricular tachycardia, ventricular fibrillation and death occur.

Barium is a physiologic antagonist to potassium and it appears that the symptoms of barium toxicity are a result of this antagonism. All of the signs of barium toxicity except hypertension are alleviated by potassium infusion. The barium ion has been shown to stimulate the release of calcitonin from the thyroid, catecholamines from the adrenal medulla, and neurotransmitter from sympathetic nerves. It also influences the electroshock sensitivity of animals. Intracerebroventricular administration produced severe convulsions and death in mice.

Reports on the effects of subchronic and chronic exposure to barium vary. Rats exposed to barium (as chloride) in drinking water at concentrations up to 250 ppm for up to 13 weeks (total barium dosage of 3,433 and 4,114 mg/kg for males and females, respectively) showed no apparent changes in physiologic parameters or health. The barium body burden increased at higher enlarged doses, but not with duration of exposure. Data provided by another study reported that exposure of female weanling rats to 1 ppm barium (as chloride) for 16 months (approximate daily intake of 0.051 mg barium/kg) in drinking water produced no effect on parameters measured (food and water intake, mean systolic blood pressure and growth) or any obvious signs of toxicity. Very small but significant ($P<0.01$) increases in mean systolic blood pressure were observed in animals exposed to 10 ppm barium for 8, 12 and 16 months (about 0.60, 0.57 and 0.51 mg barium/kg/day). A more significant ($P<0.001$) effect on mean systolic blood pressure was noted in animals exposed to 100 ppm for only 1 month (approximately 7.1 mg barium/kg/day) and at all subsequent measurements. Chickens tolerated up to 1,000 ppm barium (as acetate or hydroxide) in food for three weeks (2,625 mg/kg total estimated dosage) without apparent ill effects.

Subchronic inhalation of an unknown quantity of barium ($BaCO_3$) produced elevated arterial blood pressure, altered blood picture and decreased weight. Subchronic oral and inhalation studies of $BaCO_3$ exposure in rats indicated that barium may produce some distrubances in the reproductive system and fetotoxicity.

Exposure of rats for a lifetime to a low concentration of barium acetate (5 mg/L) in drinking water (164 mg/kg total dosage) produced no significant differences in median life-span, tumor incidence or uric acid concentrations. Changes in fasting serum glucose (males and females) and cholesterol (females), as well as proteinuria (males), were noted. Mice exposed to 5 mg/L barium acetate (587 mg/kg total dosage) in drinking water for a lifetime showed only a slight decrease in longevity.

One report on the teratogenic potential of barium in animals has been published. Introduction of 20 mg $BaCl_2$ into the yolk sac or chorioallantoic membrane of eight-day-old chicken embryos inhibited the growth of the toes in 50% of the surviving embryos. Embryos injected on day four showed no abnormalities. *In vitro* tests for possible mutagenicity showed no barium effects. Tumor production was not increased in mice or rats after lifetime exposure to 5 mg/L barium acetate (587 and 164 mg/kg total dosage, respectively) in drinking water.

VI. HEALTH EFFECTS IN HUMANS

The following section is divided into six sections: acute toxicity, chronic toxicity, teratogenicity, mutagenicity, carcinogenicity and epidemiological studies. The available data will be presented under the appropriate section with limitations of the studies noted where appropriate.

A. Acute Toxicity

Acute barium toxicity in humans due to accidental or intentional ingestion of $BaCl_2$ (Wetherill et al. 1981, Talwar and Sharma 1979, Graham 1934), $BaCO_3$ (Diengott et al. 1964, Lewi and Bar-Khayim 1964, Morton 1945, McNally 1925) and BaS (Gould et al. 1973, McNally 1925) has been described. Symptoms usually begin with rapid onset of nausea, vomiting and diarrhea due to stimulation of the GI tract musculature. Other symptoms and signs are hypokalemia, cardiac arrhythmias, cardiac pacemaker malfunctions, muscular weakness, salivation, loss of tendon reflexes, tingling, paralysis and death in the severely poisoned.

Very little information is available regarding the acute lethal dose of barium in humans. Values ranging from 0.8 g (Sollmon 1957) to 15 g (Gosselin et al. 1976) have been reported, and individuals ingesting 7 to 13 g have survived (Wetherill et al. 1981, Graham 1934). Reeves (1979) evaluated reports on barium toxicity in humans and estimated the acute lethal and threshold toxic doses for barium in adult humans to be 3 to 4 g (calculated to be 42.86 to 57.14 mg/kg for a 70-kg adult) and 0.2 to 0.5 g (calculated to be 2.86 to 71.4 mg/kg for a 70-kg adult), respectively. Reeves indicated that these values have the following limitations: (1) they are based upon the small number of human poisoning cases reported in the literature and (2) an 100% absorption of barium from the GI tract was assumed (i.e., the threshold is an exposure dose which was also assumed to be an absorbed dose).

Lewi and Bar-Khayim (1964) reported a large number of barium poisonings due to sausage contamination with $BaCO_3$. It is interesting to note that no children were brought to the hospital for treatment, and three adults who had previous gastrectomies were unaffected by consumption of the contaminated sausage. The dose of barium consumed by these subjects was not reported.

In the cases noted above, the hypokalemic response after barium ingestion was usually severe, resulting in a reduction of serum potassium from the normal range of 3.5 to 5.0 mEq/L to 1.2 to 2.7 mEq/L. Reversal of barium toxicity is accomplished by intravenous administration of potassium (Wetherill et al. 1981, Gould et al. 1973, Talwar and Sharma 1979).

Cardiac changes with barium toxicity were observed by Talwar and Sharma (1979) in a 70-year-old female after accidental ingestion of an unknown amount of $BaCl_2$. Electrocardiogram analysis revealed frequent ventricular ectopic beats, widened QRS intervals and marked ST segment elevation. The authors stated that these changes were suggestive of acute myocardial injury with a left bundle branch block pattern. Diengott et al. (1964) noted Q-T prolongation and prominent U waves in a 75-year-old male and a 62-year-old female after consumption of contaminated sausage ($BaCO_3$). A flattening of the T wave was also apparent in the 75-year-old male. This also occurred in a 26-year-old male after ingesting 15.8 g BaS (Gould et al. 1973).

Marked degeneration of the myocardium was noted at autopsy in two cases of barium salt (an unknown quantity of carbonate and sulfide) ingestion (McNally 1925). Left ventricular endocardial hemorrhage was seen after barium carbonate ingestion (Diengott et al. 1964). Severely poisoned patients developed ventricular tachycardia followed by ventricular fibrillation and death, if untreated (Roza and Berman 1971). In other cases, recovery was rapid with no complications (Gould et al. 1973, Lewi and Bar-Khayim 1964).

The ECG changes were accompanied by hypertension in all but one patient (70-year-old female), whose systolic blood pressure was 60 mm Hg upon presentation 12 hours after ingestion of $BaCl_2$ (Talwar and Sharma 1979). Elevated blood pressure (ranging from 140/80 mm Hg to 190/90 mm Hg) occurred for two days in a 52-year-old male after ingestion of 13 g $BaCl_2$, persisting even after KCl (240 mEq) had been administered and serum potassium had risen from 1.2 to 8.0 mEq/L (Wetherill et al. 1981). A 26-year-old male ingested 15.8 g BaS and had an elevated blood pressure of 110/60 mm Hg to 170/100 mm Hg (Gould et al. 1973). The blood pressure remained elevated for 6.5 hours after admission, even though 80 mEq of potassium had been administered during the first 5 hours and the cardiac murmur and paralysis of the head, neck and diaphragm abated by the sixth hour. On the third day the ECG showed normal T waves.

Barium sulfate is used as the X-ray contrast material to examine the colon. Its use has been associated with ECG abnormalities, such as T, ST and ST-T segment changes (primarily ST depression), and conduction defects, leading to arrhythmias and premature ventricular and atrial contractions (Roeske et al. 1975, Gibbs et al. 1972, Eastwood 1972, Berman et al. 1965, Stremple and Montgomery 1961). Barium sulfate is relatively unabsorbed during its brief passage through the alimentary canal. These authors agreed that the cardiovascular effects seen with barium enemas are probably not due to barium absorption, but are a function of the increased age of the patient, the presence of pre-existing cardiovascular disease and the combination of emotional, psychologic and physiologic stresses associated with the procedure.

B. Chronic Toxicity

Doig (1976) monitored adult male workers in a barite factory for lung deposition of barite ($BaSO_4$). Nine of the ten workers who were employed for more than 18 months had baritosis. The barite concentration in the air was not reported. The chest radiographs revealed dense shadows, which slowly cleared during a 12-year post-exposure period. Upon examination workers with baritosis had no symptoms, no incapacity for work, no abnormal lung function tests and no increased risk of pulmonary infections. The author concluded that baritosis represents a form of benign pneumoconiosis.

Environmental surveys were conducted to evaluate the soluble barium (chemical formula not identified) in the work atmosphere of welders (Okawa

1978). The time-weighted average exposures for soluble barium ranged from 2.20 to 6.13 mg/m^3, exceeding the 0.5 mg/m^3 standard. Exposed workers reported no adverse health effects, therefore no medical study was conducted. This report has limited value due to lack of documented medical measurements and examinations.

C. Teratogenicity

Morton et al. (1976) examined the association between 12 trace elements in the tap water and reported congenital malformations in 48 areas in Wales. Water samples containing undetectable barium concentrations (25%) were assigned an arbitrary low number for statistical purposes and a mean value of 42 µg/L (0.042 mg/L) was derived. Therefore, the negative correlation between barium concentration in tap water and congenital malformations can hardly be a valid one. No other information was located in the literature to evaluate the teratogenic potential of barium.

D. Mutagenicity

No studies evaluating the human mutagenicity of barium in humans were located in the literature.

E. Carcinogenicity

No long-term studies evaluating the carcinogenic effects of barium in humans were located in the literature.

F. Epidemiological Studies

Schroeder and Kraemer (1974) analyzed mortality rates and correlations with 35 drinking water constituents from 94 major United States cities. The mean concentration of barium was 37 μg/L (0.037 mg/L), ranging from 1.7 to 260 μg/L. They concluded that a significant negative correlation ($P<0.05$) could be drawn between high barium concentrations in drinking water and lower rates of atherosclerotic heart disease.

Elwood et al. (1974) looked for an association between 12 trace elements (identified in tap water from 48 areas in South Wales) and heart disease mortality. Only individuals 35 to 64 years of age were examined. A significant ($P<0.05$) negative correlation between barium, present at an average 0.042 mg/L, and total and cardiovascular mortality rates was discovered. These data are of limited value however, since 25% of the tap water samples contained undetectable barium concentrations and an unspecified value was assigned to these samples for statistical purposes.

Morton et al. (1976) also examined the association between congenital malformations and trace elements present in drinking water in South Wales. Although barium appeared to be negatively correlated with the incidence of congenital malformations (using Spearman's rank correlation coefficient), the linear regressions for morning and evening water samples were not significant. The trace element concentrations were the same values utilized in the Elwood et al. (1974) study and, therefore, also suffer from the same limitations.

Brenniman et al. (1979a, 1981) conducted an epidemiological study of the effects of barium in drinking water on blood pressure. Two northeastern Illinois communities selected were matched for as many demographic and socioeconomic characteristics as possible. All drinking water constituents were as identical as possible, except for the mean barium concentrations, which were 7.3 mg/L (West Dundee) and 0.1 mg/L (McHenry). There were 1,175 adults (18 years of age or older) from West Dundee and 1,203 adults from McHenry who participated in the study. For each subject, blood pressure (systolic and diastolic) was measured with an electronic apparatus three times over a twenty minute period, during which a questionnaire was completed regarding age, weight, smoking habits, family history, occupation and medication. Original analysis of the data (Brenniman et al. 1979a) indicated that there were some statistical differences in blood pressure between the communities, but application of more appropriate statistical methods (Brenniman et al. 1981) revealed that there were no significant differences ($p>0.05$) between the groups (Table VI-1). In any event, differences between the mean blood pressures (both systolic and diastolic) of age- and sex-matched groups in the two communities were small, ranging from -3.7 to 5.5 mm Hg (exposed minus control). Adjustment for duration of exposure, home water softeners and blood pressure medication did not alter the findings (Table VI-2). Such factors as smoking, obesity and occupation were found to have no relationship to this finding.

A retrospective cardiovascular mortality study (1971-1975) was conducted using age-adjusted death rates to compare communities with elevated barium concentrations (2 to 10 mg/L) to communities with little or no barium (0.0 to

Table VI-1 Age-Specific Means and Standard Deviations of Systolic and Diastolic Blood Pressure Among White Persons 18 to 75+ Years of Age Living in West Dundee and McHenry, Illinois, 1976-1977

Blood Pressure	West Dundee						McHenry					
	Male			Female			Male			Female		
Age (yr)	No. Cases	Mean (mmHg)	SD[a]	No. Cases	Mean (mmHg)	SD[a]	No. Cases	Mean (mmHg)	SD[a]	No. Cases	Mean (mmHg)	Sd[a]
Systolic												
18-24	77	123.3	13.9	114	104.6	10.2	54	120.2	12.5	53	106.1	10.6
25-34	122	123.9	13.2	147	106.5	12.3	77	122.2	12.6	111	106.4	11.9
35-44	92	123.9	16.7	133	111.6	15.0	74	124.1	15.2	88	111.3	17.0
45-54	89	127.9	16.2	91	121.3	17.5	75	129.7	15.3	90	116.3	18.6
55-64	69	131.3	21.4	75	128.1	21.1	77	135.6	17.8	136	129.5	22.3
65-74	29	139.1	20.1	60	138.1	21.0	128	140.7	21.0	137	136.2	20.4
75+	28	149.8	20.3	49	151.6	23.4	47	144.8	22.0	56	146.1	21.3
Total Pop.[b]	506	129.7	17.8	669	120.7	21.5	532	129.8	19.2	671	119.6	22.8
Diastolic												
18-24	77	73.9	10.7	114	70.1	7.9	54	71.5	10.9	53	72.9	6.7
25-34	122	76.8	10.7	147	73.4	9.9	77	78.4	10.4	111	74.6	11.0
35-44	92	82.7	10.4	133	77.3	11.5	74	82.6	11.1	88	79.6	11.6
45-54	89	84.0	11.3	91	83.5	11.1	75	85.8	11.4	90	81.5	14.1
55-64	69	82.7	13.1	75	84.4	14.9	77	86.1	12.7	136	87.0	15.1
65-74	29	82.1	13.8	60	85.8	14.5	128	85.8	13.4	137	86.6	14.7
75+	28	80.4	10.1	49	88.0	14.6	47	81.7	12.5	56	83.4	16.5
Total Pop.[b]	506	80.4	11.8	669	79.7	13.1	532	81.8	12.7	671	80.6	14.4

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[a] SD = standard deviation.

[b] Total sex-specific means are age-adjusted to the total sample size for each sex.

Adapted from Brenniman et al. (1981).

TABLE VI-2 Age-Specific Means and Standard Deviations of Systolic and Diastolic Blood Pressure Among White Persons 18-75+ Years of Age Who Do Not Have Water Softeners, Are Not Taking High Blood Pressure Medication and Have Lived More than 10 Years in West Dundee or McHenry, Illinois, 1976-1977

Blood Pressure	West Dundee						McHenry					
	Male			Female			Male			Female		
Age (yr)	No. Cases	Mean (mmHg)	SD[a]	No. Cases	Mean (mmHg)	SD[a]	No. Cases	Mean (mmHg)	SD[a]	No. Cases	Mean (mmHg)	Sd[a]
Systolic												
18-24	12	122.7	12.1	8	105.6	14.2	16	122.1	12.1	16	106.2	11.2
25-34	8	127.8	18.6	7	109.3	14.1	6	122.8	9.3	13	106.6	12.8
35-44	16	124.5	16.9	23	111.6	14.2	11	123.9	12.5	16	114.9	20.5
45-54	14	137.2	17.0	25	120.2	17.6	14	126.0	14.0	20	117.9	17.4
55-64	17	143.4	28.4	19	126.4	19.4	10	138.3	20.1	12	132.7	17.0
65-74	6	139.0	15.7	14	129.9	12.9	7	145.4	26.5	9	131.3	19.6
75+	12	152.2	19.0	20	150.9	25.4	7	138.0	21.9	7	151.1	16.2
Total Pop.[b]	85	134.6	21.6	116	121.8	22.6	71	129.9	17.8	93	122.9	20.7
Diastolic												
18-24	12	74.2	8.2	8	72.0	11.7	16	72.6	11.4	16	71.9	7.0
25-34	8	82.9	12.5	7	76.9	4.2	6	74.3	10.2	13	75.6	13.9
35-44	16	83.0	12.6	23	78.8	12.5	11	86.8	10.8	16	82.8	13.3
45-54	14	86.5	8.1	25	82.3	9.9	14	83.9	14.8	20	83.9	16.7
55-64	17	87.0	15.1	19	80.7	10.1	10	87.7	15.8	12	92.4	13.4
65-74	6	81.3	9.3	14	82.8	9.2	7	86.7	8.5	9	81.7	7.7
75+	12	79.2	11.1	20	90.5	16.3	7	79.7	11.1	7	89.8	15.9
Total Pop.[b]	85	82.1	12.0	116	80.8	12.3	71	81.9	13.4	93	83.3	14.4

[a] SD = standard deviation.

[b] Total sex-specific means are age-adjusted to the total sample size for each sex.

0.2 mg/L) in their drinking water (Brenniman et al. 1979a,b). These communities were all in northeastern Illinois and had more than 2,500 residents. Communities with high and low barium concentrations in their drinking water supplies were selected from the same counties and matched for demographic and socioeconomic status characteristics (Table VI-3). Using death certificates, the communities were screened for deaths attributable to cardiovascular diseases. These findings are shown in Table VI-4. For those death rates that were higher in the high-barium communities, a significant positive difference ($P<0.05$, using the Mantel-Haenszel test) was found in males and females combined for "all cardiovascular diseases," "heart disease" (arteriosclerosis) and "all causes." Separate analyses of males and females found a higher death rate ($P<0.05$) in the high-barium communities for male deaths from "all cardiovascular diseases," and for female deaths from "all causes."

Although the above retrospective study showed differences between communities with high and low barium concentrations in drinking water, the authors emphasized that these data should be interpreted with caution due to the following confounding factors: (1) inability to control for home water softeners and the population change during 1960 and 1970 (many residents of high-barium communities who died from cardiovascular disease were resident for less than 10 years); (2) high variability of the barium concentrations in wells containing barium in excess of 2 mg/L and consequently in barium exposure levels; and (3) inherent problems associated with a mortality study (inability to control for variables such as diet, exercise, smoking and "lifestyle" which have been implicated in cardiovascular disease). For these reasons, no conclusions regarding a NOAEL or LOAEL for barium effects can be derived from this study.

Table VI-3 General Population Characteristics of Persons Residing in Illinois Communities with High or Low Barium Levels in Their Drinking Water (U.S. Bureau of the Census, 1973)

	High-barium communities (2.0-10.0 mg/L)	Low-barium communities (0.0-0.2 mg/L)
Population	25,433	46,905
Male	12,488	22,621
Female	12,945	24,284
Non-Caucasian (%)	0.5	1.7
Under 18 years old (%)	39.1	35.8
65 years old and over (%)	7.2	9.9
Persons per household[a]	3.5	3.1
Median school years completed[a]	12.5	12.2
Mean income[a]	15,305	13,654
Median age[a]	26.5	29.7

[a] Averages of four high-barium communities (Algonquin, Crystal Lake, Lake Zurich and West Dundee) and seven low-barium communities (Antioch, Batavia, Fox Lake, Geneva, Harvard, Libertyville and Marengo).

Adapted from Brenniman et al. (1979b).

Table VI-4 Comparison of Age- and Sex-Adjusted Death Rates for Cardiovascular Diseases in Communities with Barium Levels 2.0 mg/L or Greater Against Those in Communities with Barium Levels 0.2 mg/L or Less: 1971-1975

Category	High-barium communities			Low-barium communities			Death ratio (A)/(B)
	No. of deaths		Death rates[a] (A)	No. of deaths		Death rates[a] (B)	
	Male	Female		Male	Female		
All cardiovascular disease	335	290	651.1	720	634	573.4	1.136[b]
a. Heart disease	269	206	493.9	569	451	432.0	1.143[b]
1. Arteriosclerosis	259	199	476.8	543	434	413.8	1.152[b]
2. Other	10	7	17.1	26	17	18.2	0.940
b. Cerebrovascular disease	45	62	113.1	91	137	96.5	1.172
c. General arteriosclerosis	8	8	16.7	23	20	18.2	0.918
d. Hypertension without mention of heart	2	7	9.4	6	6	5.1	1.843
e. Other circulatory disease	11	7	18.0	31	20	21.6	0.833
All causes	638	520	1148.2	1335	1109	1036.8	1.107[b]
Population (1970)	12,488	12,945		22,621	24,284		
Total person years	62,440	64,725		113,105	121,420		

[a] Deaths per 100,000 population.
[b] $P<0.05$ (for males and females combined).

Adapted from Brenniman et al. (1979b).

G. Summary

Acute human poisoning after ingestion of various barium salts produces signs and symptoms that are similar to those produced in animals with intravenous infusions of $BaCl_2$. Barium ingestion causes stimulation of the gastrointestinal musculature, resulting in salivation, nausea, vomiting and diarrhea. Skeletal and cardiac muscle stimulation follow, producing tingling, weakness, hypertension (as high as 190/90 mm Hg), arrhythmias and ECG abnormalities. Frequent ventricular ectopic beats and prolongation of the action potential have been most frequently reported. Severe cases progress to loss of deep tendon reflexes, muscular paralysis, ventricular tachycardia followed by ventricular fibrillation, and death. Hypokalemia accompanies the muscle symptoms and signs. The plasma potassium values were reduced from a normal range of 3.5 to 5.0 mEq/L to 1.2 to 2.7 mEq/L. Intravenous potassium infusion reversed the acute toxicity of barium and most subjects recovered quickly without further complications. However, the associated hypertension was not always relieved as the hypokalemia was corrected. The acute lethal dose of barium is 3 to 4 g (calculated to be 42.86 to 57.14 mg/kg for a 70-kg adult) and the threshold toxic dose is 0.2 to 0.5 g (calculated to be 2.86 to 7.14 mg/kg for a 70-kg adult).

Chronic inhalation of $BaSO_4$ by humans produced baritosis, a form of benign pneumoconiosis. No apparent adverse health effects were associated with $BaSO_4$ or "soluble" barium inhalation exposure.

The association between congenital malformations and trace elements was examined in South Wales. A negative correlation was reported for exposures at 0.042 mg/L. No other studies evaluating the teratogenicity were located in the literature. There were also no studies located in the literature to evaluate the mutagenicity or carcinogenicity of barium in humans.

Correlation between drinking water constituents and mortality rates was examined in the United States and South Wales. The mean barium content of 0.037 mg/L in drinking water from 94 major U.S. cities correlated negatively ($P<0.05$) with cardiovascular deaths. In South Wales, barium at drinking water concentrations of 0.042 mg/L also correlated negatively with cardiovascular mortality and all death rates for individuals between 35 and 64 years of age.

An epidemiological study of health effects from barium in drinking water was conducted using two matched communities in Illinois. The barium concentrations in those communities were 0.1 mg/L and 7.3 mg/L. The morbidity parameters were mean blood pressure, hypertension, cardiovascular disease, cerebrovascular disease and renal disease. There were no significant ($P>0.05$) differences in any of these parameters between the high- and low-barium communities. After adjusting for sex and mean age, some differences in mean systolic blood pressures showed a statistically significant positive correlation ($P<0.05$), but the data were inconclusive due to inconsistencies.

A retrospective cardiovascular mortality study of communities with elevated (2.0 to 10.0 mg/L) and low (0.0 to 0.2 mg/L) barium concentrations in their drinking water was reported using age-adjusted death rates. A significant increase was found ($P<0.05$) in death rates from all cardiovascular disease, heart disease (arteriosclerosis) and all causes for males and females combined in the high-barium communities. Sex-adjusted significant ($P<0.05$) increases for the high-barium populations included female deaths from all causes and male deaths from all cardiovascular diseases.

VII. MECHANISMS OF TOXICITY

This section discusses the proposed mechanism of barium action in various organ systems.

A. Cardiovascular System

The acute toxicity of barium has been documented in humans and animals. Barium has a profound effect on the electrical and mechanical activities of the musculature, producing hypertension and increased contractility and automaticity of the heart. In addition to the apparent effects on the cardiovascular system, hypokalemia develops very rapidly after barium introduction. Roza and Berman (1971) noted that the barium-induced hypokalemia could be elicited at barium infusion rates that did not produce abnormal ECG findings. Potassium measurements in the plasma and red blood cells demonstrated a significant decrease ($P<0.005$) in extracellular potassium and a concomitant increase ($P<0.01$) in intracellular potassium. The experimental protocol details of this study were discussed in Section V. A. 5., Antagonistic Action.

Alleviation of the toxic effects of barium (as measured by ECG abnormalities) in humans and animals was accomplished by intravenous administration of potassium to correct the barium-induced hypokalemia. (See Section V. A. 1., Cardiovascular System, and Section VI. A., Acute Toxicity, for more detailed discussion.) Therefore, the mechanism of barium toxicity in the cardiovascular system appears to be based on the physiologic antagonism of barium to potassium.

One symptom of toxicity that is not relieved by correcting the barium-induced electrolyte imbalance is hypertension. Two possible explanations have been proposed. One proposed mechanism involves a direct stimulatory action of barium ions on the vasculature. The other possible mechanism involves an indirect action of barium, in which barium is thought to cause the release of pressor substances in the body. These pressor substances then interact with the heart and resistance vessels to elicit the hypertensive response. Two of the most potent pressor substances in the body are epinephrine and angiotensin, released from the adrenal medulla and the renin-angiotensin system of the kidney, respectively. Elimination of the sources of these pressor agents by bilateral adrenalectomy or nephrectomy did not affect the development of hypertension after barium administration (Schott and McArdle 1974, Roza and Berman 1971). Therefore, barium appears to have a direct stimulatory influence on the heart and the smooth muscle of resistance vessels. (Details of these studies have been discussed in Section V. A. 1., Cardiovascular System.)

A more detailed analysis of the mechanism of barium toxicity is provided by studies on isolated muscle tissues. Barium ions rapidly decreased the resting membrane potential, initiated pacemaker activity and prolonged the action potential (a.p.), leading to spontaneous cardiac muscle beating, in a number of in vitro preparations. These preparations included guinea pig papillary muscles (Ehara and Inazawa 1980), dog ventricular muscle fibers (Hiraoka et al. 1980), cat papillary muscles (Mascher 1973), isolated rat hearts (Slavicek 1972), cultured embryonic chick atrial muscle cells

(Sperelakis and Lehmkuhl 1966), rabbit left atriums (Toda 1970) and guinea pig and cat right ventricular papillary muscles (Katzung and Morgenstern 1976).

Barium has been reported to convert non-pacemaker cells of quiescent embryonic chick atrial muscle (Pappano 1976) and ventricular muscle (Sperelakis and Lehmkuhl 1966) cell cultures into pacemaker cells exhibiting spontaneous depolarization and a.p. production. The cultured cells from embryonic chick ventricles exhibited synchronous contractions. Cell exposure to 5 to 10 mM $BaCl_2$ resulted in depolarization of both pacemaker and non-pacemaker cells within one minute. In addition, quiescent non-pacemaker cells developed oscillations in their membrane potentials that led to a.p. production (Sperelakis and Lehmkuhl 1966). The production of a.p. in response to electrical stimulation in embryonic chick atrial muscle cells was calcium-dependent and occurred up to day 18 of development. However, a.p. production in the absence of calcium was restored by 0.5 mM and 1.0 mM barium at times before day 18 in both cases. In addition, barium elicited the production of a.p. spontaneously, converting non-pacemaker cells to pacemaker cells (Pappano 1976). These authors agreed that depolarization of the membrane and production of a.p. (barium-induced automaticity) resulted from a barium-induced decrease in the background K^+ current and activation of the inward K^+ current.

The addition of 0.2 mmol/L barium to partially depolarized guinea pig papillary muscles increased membrane resistance, decreased the stimulus threshold and converted a graded response into a.p. production (Ehara and Inazawa 1980). The electrical and mechanical activities of the muscles treated with 0.2 or 1 mmol/L barium were strongly calcium-dependent. Addition of barium only slightly enhanced the a.p. with normal calcium (1.8 mmol/L). However, barium (>0.5 mmol/L) restored the a.p. and increased resting muscle tension when calcium was lowered to 0.2 mmol/L. The authors noted that these results suggest that the facilitating action of low concentrations of barium on the calcium-dependent slow a.p. is due to a reduction in the membrane shunting conductance and not to the development of a sizable inward barium current.

In vitro heart perfusions with calcium-free solutions have indicated that barium produces contracture of the muscle and depolarizes the membrane. In a calcium-free medium, right ventricular papillary muscles from rabbits or kittens responded to barium with increasing strength of contracture and depolarization of the membrane potential from about -35 mV to -20 mV with 0.1 and 5 mM barium (Saeki et al. 1981). Another group utilized an isolated rabbit heart preparation to study the effects of barium on heart muscle depleted of calcium, accomplished by reducing the perfusate calcium concentration from 5 to 0.078 mM (Munch et al. 1980). Addition of barium (0.5 to 1.5 mM) spontaneously increased muscle tension without producing contractions. Pressure-volume curves obtained at various barium concentrations supported a stable and graded interaction between the contractile elements of the muscle. These authors suggested that barium interacted directly with the contractile proteins of the heart in addition to influencing potassium conductance.

The studies cited above implied that barium decreases the outward passive diffusion of K^+ while apparently increasing the actively transported influx, resulting in an intracellular accumulation of K^+. The antagonism of potassium movement across the cellular membrane by barium may be a result of the similarity of the atomic radii of barium (1.34 Å) and potassium (1.33 Å) (Armstrong and Taylor 1980). These actions are in complete agreement with the barium-induced hypokalemia seen in physiologic studies. However, studies relating barium exposure to cardiovascular effects in humans are limited to acute, high dosage incidents, and it is difficult to extrapolate to chronic human toxicity.

B. Striated Muscles

Acute barium exposure in animals and humans initially stimulates striated muscles, producing twitching. This is followed by flaccid paralysis. Rat leg muscle contraction measurements demonstrated progressive development of paralysis. This correlated well with the time course of barium-induced hypokalemia, but not with barium concentrations in plasma (Schott and McArdle 1974). This paralysis was demonstrated by direct electrical stimulation of muscle and indirect stimulation via the nerve. The experimental protocol details of this study were presented in Section V. A. 2., Striated Muscles.

Sperelakis et al. (1967) showed that isolated sartorius muscle fibers of the frog (R. pipiens) bathed in media free of chloride ions (where K^+ movement provides a major contribution to conductance) rapidly responded to 0.05 to 5.0 mM barium with depolarization, spontaneous contractions (fibrillations), and prolonged a.p. These responses began within 0.5 minute after barium addition and were reversed by the addition of SO_4^{-2} to precipitate the barium. The effect of barium on the K^+ conductance in a hypertonic sucrose solution (where

Na^+ contributes a significant part of the total membrane conductance) was compared to that in a Cl^--containing solution with a high K^+ concentration. Although the K^+ concentrations differed by a factor of about 33, barium produced approximately the same proportional decrease in K^+ conductance. Therefore, the conclusion was that barium appears to act as a competitive inhibitor of the membrane movement of K^+. Consequently, the mechanism of barium toxicity in striated muscle appears to be identical to that in cardiac muscle and is based on its antagonism to K^+.

C. Nervous System

Barium produces convulsions in mice when administered intracerebrally and affects the electroshock threshold for convulsions after intraperitoneal administration (see Section V. A. 3., Nervous System, for details). Barium (20 mg/kg, intraperitoneally) initially increased convulsive electroshock sensitivity (at 0.5 hour) and then decreased sensitivity (at 24 hours). Barium distribution in subcellular fractions of brain was relatively constant at 0.5 hour. At 24 hours the concentration of barium increased, especially in the mitochondrial fraction (Peyton and Borowitz 1978). Mitochondrial uptake of barium did not affect the mitochondrial calcium concentration.

Although definitive studies on the mechanisms of action of barium in the CNS have not been reported, the initial increased excitability produced by barium is consistent with the increased excitability due to membrane depolarization seen in other tissues. The depression of convulsive electroshock sensitivity coincided with an increased barium and calcium content in subcellular fractions of the brain. Increased calcium depresses neuronal activity, and barium may mimic calcium in some tissues. It is interesting to note that pretreatment with atropine or naloxone protected the animals from barium-induced convulsions and lethality.

In vitro studies of peripheral nerves indicated that myelinated fibers are much more susceptible to barium than unmyelinated fibers. Lorente de No and Feng (1949) showed that low concentrations of barium (0.0037 to 0.043 M) depolarized myelinated (A fibers) and unmyelinated (C fibers) nerves and produced spontaneous slow potential activity. The magnitude and rate increased with the barium dosage. Higher concentrations produced blockade of conduction, first in A fibers and then in C fibers. Greengard and Straub (1959) also examined barium effects on A fibers of the frog tibial nerve and B and C fibers of the rabbit cervical sympathetic trunk. The electrically stimulated a.p. of A fibers was abolished in about five minutes when bathed in an isotonic solution of $BaCl_2$. However, B and C fibers in isotonic $BaCl_2$ generated a.p. that were nearly 3 times greater in amplitude and more than 100 times longer in duration than controls.

Another report dealt with the interaction of barium ions with K^+ channels in squid giant axons (Armstrong and Taylor 1980). Evidence presented suggests that, due to the similarity of the crystal radii of barium (1.34 Å) and potassium (1.33 Å), intracellular and extracellular Ba^{+2} is able to enter K^+ channels and produce blockade. This blockade is antagonized by increasing the intracellular or extracellular K^+ concentration.

D. Secretory Processes

Calcium plays a critical role in the phenomenon of stimulus-secretion coupling. This is involved in such processes as conduction of nerve impulses across the synapse and release of catecholamines from the adrenal medulla (Douglas 1968, 1976, Rubin 1970, Douglas and Rubin 1963). Evidence suggests that barium can partially mimic calcium and influence these events. The details of the following studies were presented in Section V. A. 4., Secretory Processes. Intravenous administration of $BaCl_2$ increased plasma levels of the thyroid hormone calcitonin by a factor of 2.5 in one experiment and a factor of 5 in another (Pento 1979). Barium-induced secretion of calcitonin was also demonstrated in the isolated whole thyroid and thyroid slices. *In vivo* perfusion studies demonstrated that barium could substitute for calcium in eliciting catecholamine release from the adrenal gland and produced an intense secretory response (Douglas and Rubin 1964a,b). Additionally, barium increased the calcium-stimulated secretion. Barium also substituted for calcium in eliciting norepinephrine release from electrically stimulated sympathetic nerves (Kirpekar and Misu 1967). Barium-induced secretion was higher than calcium-induced secretion and continued in these preparations even after barium removal.

Other *in vitro* studies support the ability of barium to mimic and substitute for calcium in secretory processes. Substitution of 1.8 mM barium for 1.8 mM calcium caused quantal acetylcholine release from the nerves at the frog neuromuscular junction. This resulted in muscle fibrillation and a decrease in the muscle membrane potential over a 15- to 30-minute period

(Silinsky 1978). In addition, electrical stimulation in the presence of 1.8 mM barium elevated the frequency of miniature endplate potentials (m.e.p.p.) to 5 to 20 times the control frequency (1.8 mM calcium). The number of acetylcholine quanta released asynchronously by nerve impulses was directly related to the external barium concentration in a nonlinear fashion. Barium was two orders of magnitude more effective than calcium in supporting the evoked m.e.p.p. discharge. Also, calcium was a potent antagonist to release in barium solutions, and vice versa. Therefore, barium appeared to traverse the same conductance pathway normally traversed by calcium.

In contrast to calcium, barium induced asynchronous acetylcholine release and did not appear to be able to unify the release into an impulsive event and mimic response to the nerve a.p. Barium also substituted for calcium in releasing norepinephrine from guinea pig vas deferens that had been exposed to high K^+ concentration (Nakazato 1980). In the absence of excess K^+, barium had no effect on norepinephrine release.

The mechanisms of barium-induced adrenal catecholamine release were examined in isolated perfused bovine adrenals (Shanbaky et al. 1978). Barium chloride (5 mM) evoked catecholamine release that was five times higher than the control at one minute after exposure. Since the cytoplasmic enzyme lactate dehydrogenase was not released, barium-induced release of catecholamines was probably not a result of cell disruption. Barium appeared to accumulate in the mitochondria but did not affect the distribution of adrenomedullary ^{45}Ca. The lack of effect of barium on the metabolism of calcium is an argument against the involvement of intracellular calcium in the action of barium. Studies in which barium induced secretion in the absence of calcium provide evidence against extracellular calcium being the barium mediator in the response. Therefore, barium appears to alter the membrane to gain entry into the cell, where it mimics calcium and influences secretory processes.

E. Teratogenicity, Mutagenicity and Carcinogenicity

No studies evaluating the mutagenicity or carcinogenicity of barium compounds in humans have been reported in the literature. A single report of teratogenic effects in chick embryos did not investigate the mechanism of action of barium.

F. Summary

The mechanism of acute barium cardiovascular toxicity is based on the physiologic antagonism of barium to K^+. Barium ions interact with cellular membranes to decrease the outward passive diffusion of K^+ from the cells while increasing the active inward transport of K^+ possibly due to the similarity of the atomic radius of barium (1.34 Å) and potassium (1.33 Å). The end results of these effects are a rapid transfer of K^+ from the plasma to the intracellular compartment, a decrease in the resting membrane potential, an initiation of pacemaker activity and prolongation of a.p., producing increased automaticity and contractility.

Studies in calcium-free solutions suggest that barium may also interact directly with the contractile proteins in the heart. Hypertension is apparently a result of direct stimulation by barium of the cardiac musculature and the smooth muscle of resistance vessels. All signs of acute barium toxicity in the cardiovascular system except hypertension are alleviated by correcting the hypokalemia with K^+ infusion. There are no studies examining the possible role of barium in producing hypertension in humans.

Striated muscles exhibit an early stimulation when exposed to barium, followed by progressive paralysis. The time course of paralysis closely parallels that of hypokalemia. *In vitro* experiments demonstrate that initial muscle stimulation is due to a barium-induced decrease in K^+ conductance.

Although barium produced convulsions when introduced intraventricularly and influenced convulsive electroshock sensitivity after intraperitoneal administration, the mechanism of action of barium in the CNS was not determined. However, peripheral nerves acutely exposed to barium demonstrate a decrease in membrane potential, depolarization and, finally, blockade of conduction with increasing barium concentrations. These effects were shown to be due to decreased K^+ conductance and could be antagonized by increasing the K^+ concentration. Therefore, barium antagonism of K^+ appears to be the basis for acute barium toxicity to peripheral nerves.

The chemical properties of the barium ion seem to allow barium to enter the cell and replace or mimic calcium in a number of processes mediated by calcium. Barium infusion was shown to increase plasma calcitonin levels.

Barium elicited catecholamine release from the adrenal medulla, norepinephrine release from sympathetic nerve endings, and catecholamine release from motor nerves in the absence of calcium. Isolated tissue studies demonstrate that barium does not affect calcium metabolism in the adrenal medulla. This argues against intracellular calcium involvement in the barium action. The effect of barium on the membranes in these preparations was not determined.

There were no studies evaluating the teratogenicity, mutagenicity or carcinogenicity of barium in humans.

The mechanisms of barium toxicity are derived from acute, high dosage exposure in animals and *in vitro* experimentation. Although these reports may provide a basis for understanding possible chronic effects, it is difficult to extrapolate these effects and mechanisms of barium toxicity to chronic animal or human barium exposure.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the non-carcinogenic and carcinogenic effects. In the quantification of non-carcinogenic effects, an Acceptable Daily Intake (ADI) is calculated. From this an Adjusted Acceptable Daily Intake (AADI) and Health Advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{\text{(NOAEL or LOAEL in mg/kg/day)(Body Weight in kg)}}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{Drinking Water Volume in L/day}} = \text{mg/L}$$

where:

NOAEL = no-observed-adverse-effect level.

LOAEL = lowest-observed-adverse-effect level.

Body weight = 70 kg for adult or 10 kg for child.

Drinking water volume = 2 L per day for adults or 1 L per day for children.

Uncertainty/Safety Factor = 10, 100 or 1,000.

Utilizing these equations, the following drinking water concentrations are developed for non-carcinogenic effects:

1. A one-day HA for 10-kg child.
2. A one-day HA for 70-kg adult.
3. A ten-day HA for 10-kg child.
4. A ten-day HA for 70-kg adult.
5. A lifetime AADI for a 70-kg adult.

The distinctions made between the HA calculations (items 1 through 4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited period of exposure (possibly 1 to 2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon non-carcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivity to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS 1977, 1980) is typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data identifying a NOEL/NOAEL are available and are supported by acute or chronic toxicity data in other species.

- An uncertainty factor of 100 is used either when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more animal species (but human data are not available), or when good acute or chronic toxicity data identifying a LOAEL in humans are available.

- An uncertainty factor of 1,000 is used either when limited or incomplete acute or chronic toxicity data are available, or when good acute or chronic toxicity data identify a LOAEL (but not a NOEL/NOAEL) for one or more animal species.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines for selection of an uncertainty factor, but must be considered include: (1) the quality of the toxicology data, (2) the significance of the adverse effect and (3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen (there is insufficient evidence to classify barium as a carcinogen following ingestion), mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical via drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans from these data, it must be converted to an equivalent human dose. This conversion includes correction for non-continuous animal feeding, non-lifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 liters of water per day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and random error. In most cases, only studies using experimental animals have been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as (1) incomplete knowledge concerning the health effects of contaminants in drinking water, (2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results and (3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

A. Non-Carcinogenic Effects

Gastrointestinal absorption of barium in animals varies widely (from 5% to 85%), depending on the species, contents of the gastrointestinal tract and age. Absorption in fasted rats (6 to 8 weeks old) was three times that of fed rats. Weanling rats absorbed 85% of an oral dose of barium, while adult rats absorbed approximately 7%. Concurrent administration of milk sugar (lactose) and lysine significantly ($P<0.05$) increased barium absorption in fasted adult rats. The ICRP Committee II Report on Permissible Dose for Internal Radiation reported a gastrointestinal absorption factor of 5% for reference man. The National Academy of Sciences Safe Drinking Water Committee has evaluated the limited data available and estimated that 20% represents a conservative estimate of the gastrointestinal absorption for barium in humans. However, no definitive barium absorption studies in humans were located in the literature. Information is specifically lacking on barium absorption in human children to determine if the observations in young and adult rats apply to the human (see Section III for greater detail).

1. Short-Term Exposure

Roza and Berman (1971) induced barium toxicity in mongrel dogs (6 to 22 kg, both sexes) by intravenous infusion of $BaCl_2$. An infusion of 1 µmol/kg/min (approximately 0.137 mg Ba/kg/min) produced the following signs of barium toxicity: hypokalemia, hypertension, and premature supraventricular and ventricular contractions within five minutes (total of 0.685 mg Ba/kg), followed by skeletal muscle contractions, salivation, diarrhea and multiple premature ventricular tachycardia, fibrillation and death. Higher infusion rates (i.e., greater than 4 µmol/kg/min or 0.548 mg Ba/kg/min) produced paralysis and death within a few minutes. In another study, thirteen dogs were infused with 22 to 154 µmol $BaCl_2$/kg (3.01 to 21.1 mg Ba/kg) at rates ranging from 0.5 to 2.0 µmol/kg/min (0.069 to 0.274 mg Ba/kg/min) over periods of 20 to 100 minutes. Infusion of barium was terminated at the appearance of abnormal ECG findings. Pronounced hypokalemia (0.3 to 2.1 mEq/L, $P<0.005$) was observed with a concomitant increase ($P<0.01$) in red cell potassium content. The authors noted that no correlation between the barium dosage and the degree of hypokalemia was apparent. Although this study demonstrates the steep toxicity curve associated with barium, no minimum-adverse-effect level of barium could be extrapolated.

Although controlled studies of acute barium toxicity have not been performed in humans, accidental poisonings and suicide attempts have provided information on the acute effects of barium ingestion.

Wetherill et al. (1981) described symptoms of abdominal pain, intractable diarrhea and weakness in a 52-year-old male eight hours after ingestion of 13 g $BaCl_2$. These symptoms were followed closely by the development of hypokalemia (1.2 mEq/L), progressive paralysis and hypertension (190/90 mm Hg). After intravenous potassium infusion (240 mEq), the patient recovered but remained hypertensive for two days after correction of the hypokalemia.

Electrocardiographic analysis of a 70-year-old female who had ingested an unknown quantity of $BaCl_2$ was reported by Talwar and Sharma (1979). Twelve hours after ingestion, the ECG revealed frequent ventricular ectopic beats, widened QRS intervals and marked ST segment elevation. Systolic blood pressure was 60 mm Hg and gastrointestinal disturbances were apparent. Potassium chloride was infused (serum potassium was 2.5 mEq/L), but two hours after admission cardiac arrest ensued. Resuscitation measures were unsuccessful.

Reeves (1979) has evaluated the above and other human case reports and estimated the threshold toxic dose of barium in adult humans to be 0.2 to 0.5 g (approximately 2.9 to 7.1 mg Ba/kg for a 70-kg adult). Reeves indicated that these values have the following limitations: (1) they are based upon the small number of human poisoning cases reported in the literature and (2) 100% absorption of barium from the GI tract was assumed (i.e., the threshold is an exposure dose which was also assumed to be an absorbed dose).

2. Long-Term Exposure

Schroeder and Mitchener (1975a,b) exposed random-bred Long-Evans rats (75 to 80 days old) and Charles River CD Swiss mice (19 to 20 days old) to 5 mg/L (approximately 0.25 and 0.825 mg/kg/day, respectively) barium (as the acetate) in drinking water for a lifetime. There were 52 rats and 54 mice of each sex in the experimental groups. No differences were noted in median life span, tumor incidence or serum uric acid concentrations. There was an increase in proteinuria (males), a decrease in fasting serum glucose (males and females) and an increase in fasting serum cholesterol (females) in exposed rats when compared to controls at various time intervals. In barium exposed mice, there was no toxicity in terms of growth, edema, blanching of incisor teeth or tumor incidence. Male mice, but not female mice, showed a slight reduction ($P<0.025$) in longevity (defined as the mean age of death of the last surviving 10% of the animals, or in this case, of 5 animals) when compared to controls. This study is of limited usefulness in estimating the NOAEL for barium, since only a single dose was tested.

Tardiff et al. (1980) exposed groups of five to ten Charles River rats (95 to 136 g) of each sex to barium (as barium chloride) in drinking water for 4, 8 and 13 weeks. The barium concentrations were 0, 10, 50 and 250 ppm (approximately 0, 2.75, 13.7 and 66.25 mg Ba/kg/day, respectively, at the beginning of the study and 0, 1.7, 6.6 and 31.5 mg Ba/kg/day, respectively, at the end of the study). No adverse effects on food consumption, body weight, hematologic parameters, serum ions (K^+, Na^+, Ca^{+2}), serum enzymes, gross pathology or histopathology were observed. The relative weights of the adrenals were significantly ($P<0.05$) less than controls in males treated for 8 weeks at 50 and 250 ppm barium and females treated 8 and 13 weeks at 250 ppm barium. However, the effect did not appear to be dose-related in either sex. The 250 ppm (66.25 to 31.5 mg/kg/day) barium groups also consumed less water than controls or other experimental animals. In comparison to the 250 ppm barium groups, male controls consumed 43 and 11 mL/kg/day more water and female controls consumed 63 and 11 mL/kg more water at the beginning and end of the study, respectively. Although the barium body burden increased (as discussed in Section III, Toxicokinetics) with increasing barium dosage, no conclusive signs of barium toxicity were produced in these animals. Thus, the NOAEL in this study was 31.5 mg Ba/kg/day.

Perry et al. (1983) exposed female weanling rats to 1, 10 or 100 ppm barium (administered as $BaCl_2$) in drinking water for up to 16 months (an average daily barium dose of 0.051, 0.51 and 5.1 mg/kg, respectively[a]). Weight and systolic pressure measurements were made at 1 month for the "1 month" populations, at 2 and 4 months for the "4 month" populations and at 8,

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[a] The authors presented average daily water intakes and weights. Therefore, the daily barium dose was estimated by the following calculation:

$$\frac{\text{daily water intake (L/day) x barium concentration (mg/L)}}{\text{weight (kg)}} = \text{mg/kg/day}$$

12 and 16 months for the "16 month" populations. Each exposure group consisted of 12 to 13 animals, and each exposure period had 21 controls. The average animal weights were 0.17, 0.228, 0.301, 0.348, 0.405 and 0.435 kg for the 1, 2, 4, 8, 12 and 16 month populations. There were no obvious signs of toxicity or changes in mean water or food intake at any barium dose levels when compared to controls.

Animals exposed to 1 ppm barium for 1 to 16 months (average dose range from 0.071 to 0.051 mg Ba/kg/day, respectively) had no changes in mean systolic blood pressure when compared to controls. Animals exposed to 10 ppm barium were observed to have small but significant ($P<0.01$) increases in mean systolic pressure of 6, 7 and 4 mm Hg over controls after 8, 12 and 16 months, respectively (approximately 0.60, 0.57 and 0.51 mg Ba/kg/day). The 100 ppm barium-exposed animals (approximately 7.1 mg Ba/kg/day) had a significant increase ($P<0.001$) in mean systolic blood pressure which averaged 12 mm Hg after one month. Systolic blood pressure in the 100 ppm barium groups was consistently increased during all subsequent measurements, reaching 16 mm Hg over controls at 12 and 16 months (approximately 5.7 and 5.1 mg/kg/day, respectively). For rats sacrificed at 1, 4 and 16 months, there were no differences in metal content of the heart (Ba, Ca, Mg, K, Na) or average cardiac weight except for a significant increase ($P<0.001$) in barium concentration in the heart of animals from the 100 ppm dose group. Rats exposed to 100 ppm barium for 16 months had depressed rates of cardiac contraction and depressed electrical excitability. For these rats, the barium-induced increase in mean systolic blood pressure was evident under ketamine and xylazine anesthesia but absent with pentobarbital (45 mg/kg). In the rats exposed to 100 ppm barium for 16 months, cardiac ATP, phosphocreatine and phosphorylation potential were decreased, and ADP was suggestively increased (as measured by ^{31}P-NMR spectroscopy). No measurements of contractility, conduction velocity or phosphate metabolites were made in the rats exposed to 1 or 10 ppm barium.

The EPA has considered this data and decided that the increase of 4 mm Hg in blood pressure seen after 16 months in animals ingesting 0.51 mg Ba/kg/day is not large enough to constitute an adverse health effect. Therefore, the NOAEL in this study is 0.51 mg Ba/kg/day, and the LOAEL is 5.1 mg Ba/kg/day. A limitation of this study is the minimized exposure to other metals in the food, water and laboratory environment. Because of the interactions of barium with other trace metals, the restricted exposure to other metals may have contributed to the toxicity of barium. It is apparent that further work is required to clarify whether an association exists between chronic barium exposure and hypertension in animals ingesting a normal diet.

An epidemiological study of barium health effects was conducted using two matched communities in Illinois having 0.1 and 7.3 mg/L barium in their drinking water (Brenniman et al. 1979a, 1981). There were 1,175 adults from the high-barium community and 1,203 adults from the low-barium community who participated in the study. In the study report (Brenniman et al. 1979a), no significant differences (P>0.05) were reported in mean systolic and diastolic blood pressures between all male and female adults (18 years of age or older) in these communities. After adjusting for sex and mean age, the authors originally concluded (Brenniman et al. 1979a) that some differences in mean systolic blood pressure were significant ($P<0.05$) for the high-barium community. However, during peer review of the study report concerns were expressed with the statistical analysis procedures. Based upon recommendations received during the peer review, a more appropriate statistical analysis was performed and this failed to demonstrate a significant difference between blood pressure in the two populations (Brenniman et al. 1981). In any event, differences between the mean blood pressures of age- and sex-matched groups in the two communities were small, ranging from -3.7 to 5.5 mm Hg (exposed minus control). Adjustment for duration of exposure, home water softeners, and anti-hypertensive drugs did not alter this finding. Thus, the exposure level of 7.3 mg/L barium in the drinking water is judged to be a NOAEL from this study.

A retrospective mortality study of communities in Illinois with high (2.0 to 10.0 mg/L) and low (0.0 to 0.2 mg/L) barium concentrations in their drinking water was reported using age-adjusted death rates (Brenniman et al. 1979a,b). Significant ($P<0.05$) increases in death rates from all cardiovascular disease, heart disease (arteriosclerosis) and all causes were reported for the high-barium communities when compared to the low-barium populations. Significant increases ($P<0.05$) were also reported for deaths of females from all causes and for deaths of males from all cardiovascular disease in the high-barium communities. The authors emphasized that these data should be interpreted with caution due to the following confounding factors: (1) inability to control for home water softeners and the population change during 1960 and 1970 (many residents of high-barium communities who died from cardiovascular disease were resident for less than 10 years); (2)

high variability of the barium concentrations in wells containing barium in excess of 2 mg/L and consequently in barium exposure levels; and (3) inherent problems associated with a mortality study (inability to control for variables such as diet, exercise, smoking and "lifestyle" which have been implicated in cardiovascular disease). For these reasons, no conclusions regarding a NOAEL or LOAEL for barium effects can be derived from this study.

B. Quantification of Non-Carcinogenic Effects

1. One-Day Health Advisory

No suitable studies were found in the literature to calculate a one-day HA for children or adults.

2. Ten-Day Health Advisory

No suitable studies were found in the literature to calculate a ten-day HA for children or adults.

3. Adjusted Acceptable Daily Intake

Several studies merit consideration as the basis for calculation of the ADI and AADI for barium. Tardiff et al. (1980) found that 250 ppm barium in water (about 31 to 65 mg Ba/kg/day) produced no effect in rats in 13 weeks. However, this study was not long-term (lasting only 91 days), and in addition, blood pressure was not monitored.

The studies by Schroeder and Mitchner (1975a,b) suggest that 5 ppm barium in water (lifetime exposure) might be a LOAEL in rats and mice (corresponding to doses of about 0.25 and 0.85 mg Ba/kg/day, respectively). However, observed effects were minor, and an apparent effect on longevity was based on only five animals.

Perry et al. (1983) demonstrated that 10 ppm barium in water supplied to rats (0.51 mg Ba/kg/day) produced a small (but statistically significant) increase in blood pressure by 8 to 16 months. It is judged by the EPA that this increase (4 to 7 mm Hg) is not large enough to be considered an adverse effect. Water containing 100 ppm barium (5.1 mg Ba/kg/day) produced clear hypertension and cardiotoxic effects. Thus, 0.51 mg/kg/day represents the NOAEL, and 5.1 mg/kg/day represents the LOAEL in this study. The principal disadvantage of this study is that the animals were maintained in a special environment and received a special diet and special water, all designed to reduce exposure to trace metals. Because of the beneficial effects of some metals and the interactions of barium with other metals, it is possible that the restricted intake of other metals may have contributed to the apparent toxicity of barium.

Brenniman et al. (1981) performed an epidemiological study in humans and concluded that there was no statistically significant effect on blood pressure in people ingesting drinking water containing 7.3 mg Ba/L compared to people ingesting water containing 0.1 mg Ba/L. This corresponds to a dose of 0.20 mg Ba/kg/day (assuming a 70-kg adult drinks 2 L per day). Because of uncertainties regarding this study, the EPA solicited outside reviews of the work. It was concluded that there were significant flaws in the sampling design and data analysis, and that this study is not appropriate for derivation of an AADI.

Thus, none of the candidate studies are free of difficulties. The study by Perry et al. (1983) has been selected as the one which is most appropriate because: (1) it established a clear dose-response relationship between barium exposure and adverse effects; and (2) increased blood pressure was measured, and this appears to be the most sensitive index of barium toxicity. The LOAEL identified in this study was 5.1 mg/kg/day.

The ADI for a 70-kg adult is calculated as follows:

ADI:

$$\frac{(5.1\ \text{mg/kg/day})\ (70\ \text{kg})}{100} = 3.57\ \text{mg/day}$$

where:

5.1 mg/kg/day = LOAEL, based on an increase in blood pressure in rats (Perry et al. 1983).

70 kg = assumed body weight of an adult.

100 = uncertainty factor. According to NAS/ODW guidelines, an uncertainty factor of 1,000 is appropriate for use when a LOAEL from an animal study is employed. However, a major limitation of this study is the minimized exposure to trace metals (e.g., Ca) in the food, water and laboratory environment, and this may have

contributed to the observed effects. To accommodate for this, the EPA feels that selection of an uncertainty factor of 100 is more appropriate.

The AADI for a 70-kg adult is calculated as follows:

AADI:

$$\frac{(3.57\ \text{mg Ba/day})}{2\ \text{L/day}} = 1.79\ \text{mg Ba/L}$$

where:

3.57 mg Ba/day = ADI (based on Perry et al. 1983)

2 L/day = assumed water consumption by a 70-kg adult.

This AADI calculation assumes 100% of the human exposure derives from drinking water. This value may be modified upon the availability of relative source contribution data which provide estimates of human exposure from food, air and possibly the occupational environment.

C. Carcinogenic Effects

No information was located in the available literature regarding the carcinogenic potential of barium in humans. Schroeder and Mitchener (1975a,b) exposed Swiss Charles River CD mice and random-bred Long-Evans rats to 5 mg/L barium acetate (estimated barium dosage of 0.825 and 0.25 mg/kg/day, respectively) in drinking water during a lifetime study. Upon macroscopic examination, there was no increased incidence of tumors in the exposed animals over the controls.

The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenic potential of barium (WHO 1982).

D. Quantification of Carcinogenic Effects

Due to the absence of toxicology evidence to classify barium as a potential carcinogen, a quantification of carcinogenic risks for barium cannot be made.

E. Existing Guidelines and Standards

The National Academy of Sciences (NAS 1982) derived a revised chronic Suggested No-Adverse-Response Level (SNARL) value for barium of 4.7 mg/L. They state that there are no adequate direct data from which to calculate a chronic SNARL for barium, but believe that their derived value of 4.7 mg/L provides adequate safety for chronic exposure. This value was derived assuming a 20% gastrointestinal absorption rate for barium in the adult human. (This assumption was required because the calculation was based upon inhalation data.) However, animal studies (Taylor et al. 1962) indicate that young rats absorbed 85% of an administered oral dose of barium compared to 7% absorption in adult animals. Therefore, the NAS SNARL may not adequately address the greater absorption rate estimated for the younger segment of the population. If the chronic SNARL is recalculated according to NAS (1982) using values which are more appropriate for children (80% absorption, 1 L of water per day), the resulting value is 2.3 mg/L. It should be noted that the AADI of 1.79 mg/L calculated in this Criteria Document is below this value, indicating that children may also be protected at these levels.

The American Conference of Governmental Industrial Hygienists established an occupational threshold limit value (TLV) of 0.5 mg/m^3 for barium nitrate (ACGIH 1980). The TLV represents a maximum average concentration of a substance in the work place air which presents no hazard to the health or well-being of the workers during their lifetime.

The National Interim Primary Drinking Water Regulations of 1975 established a Maximum Contaminant Level (MCL) water standard for barium of 1 mg/L (USEPA 1976b). This value was derived from the work of Stokinger and Woodward (1958). These researchers assumed an eight-hour daily exposure (10 m^3 of air) with a 75% lung absorption rate. Using the TLV of 0.5 mg/m^3, they calculated a respiratory delivery of 3.75 mg/day of barium into the blood, as follows:

$$10\ m^3 \times 0.5\ mg/m^3 \times 0.75 = 3.75\ mg$$

This absorbed dose was presumed to be noninjurious to health and was adopted as the maximum daily dose that should be taken into the body by any route of exposure. Calculation of the drinking water standard was derived using estimates of GI absorption and daily water intake, assumed to be 90% and 2 L/day, respectively:

$$3.75\ mg/day \times \frac{1}{0.9} \times \frac{1}{2\ L/day} = 2.085\ mg/L$$

Thus, a barium concentration of 2 mg/L in drinking water was considered safe for most adults. Since this calculation was based on a healthy, homogeneous population of workers, a safety factor of two was incorporated to protect more susceptible subpopulations. The resultant standard derived for barium was 1 mg/L. Therefore, the 1 mg/L drinking water standard for barium was not based on any toxicological study, was adapted from inhalation limits rather than from oral exposure data and is based on undocumented oral and inhalation absorption values.

The USSR standard for waterborne barium is 4 mg/L (NAS 1977). No other international barium drinking water standards were located in the available literature.

The World Health Organization (WHO 1983) has not established a guideline value for barium in drinking water. They state that there is a lack of firm evidence of any health effects associated with "normally low levels" of barium in water and only weak evidence of health effects at 10 mg/L.

F. Special Considerations

1. Populations at Risk

Subchronic studies, previously described in Section V, document a direct relationship between exposure to barium and barium body burden. Thus, populations that are exposed to high natural levels of barium in drinking water are a sub-group at increased risk.

2. Sensitive Populations

The study of Perry et al. (1983) indicates that increased blood pressure occurs in animals after chronic barium exposure, and, therefore, humans with elevated blood pressure may constitute an especially sensitive segment of the population. Because cardiovascular disease is common in the United States, with over 35 million Americans having hypertension (National Center for Health Statistics 1983), it seems prudent to give special consideration to this population with regard to barium toxicity.

Age differences in barium absorption have been described in Section III (e.g., Taylor et al. 1962). Very young animals absorbed barium at a significantly greater rate than adults (85% versus <10%). The greater (relative to body weight) fluid intake in very young animals may further compound this effect. Therefore, a smaller relative dose may be required to induce toxic effects in children than in adults.

Dietary factors, such as fasting, are known to affect barium absorption from drinking water. The study by Taylor et al. (1962), discussed in Section III., demonstrated a threefold increase in barium absorption following an 18-hour fasting period. Extended fasting is not common in the U.S. population lifestyle. Therefore, this factor was not considered relevant to the quantitative risk assessment.

Other dietary factors, including types, quantities and frequencies of food ingested, may also affect the amount of barium entering the circulatory system. The study by Lengemann (1959), discussed in Section III., demonstrated that barium absorption in 24-hour fasted adult rats increased by a factor of approximately three in the presence of lactose (a sugar present in milk) and approximately four in the presence of lysine. Milk consumption by adults may vary, but milk usually represents an important fraction of the total diet and daily fluid intake in infants and children. The consumption of milk is maximal at 5 to 6 months of age (average of 900 mL/day) and declines to about 190 mL/day at age 60 years or more (ICRP 1975). Therefore, milk drinkers, especially younger individuals who have a comparatively greater milk consumption, may represent a sub-group more sensitive to barium toxicity.

Based on the preceding discussions, the following subgroups of the population should be considered more sensitive to the toxic effects of barium than the general population: (1) those suffering from disorders of the cardiovascular system (especially hypertension), (2) children, (3) individuals who are fasting or who have low food intake and (4) individuals consuming large quantities of milk or milk products. These factors are believed to be accounted for in the ADI and AADI calculations by the application of the appropriate uncertainty factors. Of specific importance are children who are believed to have a higher absorption rate of barium than adults.

3. Interactions

No studies of the interaction between barium and other compounds were located in the available literature. Therefore, there is insufficient data to permit consideration of potential interactions (i.e., synergistic/antagonistic effects) in the AADI calculation.

C. Summary

The recommended value for the AADI is summarized in Table VIII-1.

Table VIII-1 Summary of Quantification of Toxicological Effects of Barium

	Barium drinking water concentration, mg/L		
	10-kg Child	70-kg Adult	Reference[a]
One-Day Health Advisory	–[b]	–[b]	-
Ten-Day Health Advisory	–[b]	–[b]	-
AADI	–[c]	1.79	Perry et al. (1983)

[a] Reference for NOAEL or LOAEL used as the basis for the calculation.
[b] Not calculated because there is insufficient data on short-term effects.
[c] Not calculated because the child will not remain in the high risk population for a lifetime.

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